PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6: C07D 403/14, A61K 31/41, C07D 417/14, 413/14, 403/06, 417/06, 413/06 — A1

(11) International Publication Number: **WO 95/08550**

(43) International Publication Date: 30 March 1995 (30.03.95)

(21) International Application Number: PCT/US94/10049

(22) International Filing Date: 7 September 1994 (07.09.94)

(30) Priority Data:

08/126,822	24 September 1993 (24.09.93)	US
08/295,441	29 August 1994 (29.08.94)	US

(71) Applicant: ABBOTT LABORATORIES [US/US]; CHAD 0377/AP6D-2, One Abbott Park Road, Abbott Park, IL 60064-3500 (US).

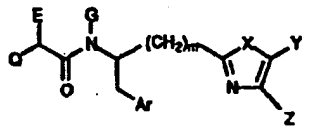
(72) Inventors: vonGELDERN, Thomas, W.; 4209 W. Solon Road, Richmond, IL 60071 (US). KESTER, Jeffrey, A.; 680 Sapling, Deerfield, IL 60015 (US). ROSENBERG, Saul, H.; 15 Lighthouse Lane, Grayslake, IL 60030 (US). WINN, Martin; 1263 Carlisle Place, Deerfield, IL 60015 (US). HUTCHINS, Charles, W.; 4120 Oglesby, Gurnee, IL 60031 (US).

(74) Agents: CROWLEY, Steven, R. et al.; Abbott Laboratories, CHAD 0377/AP6D-2, One Abbott Park Road, Abbott Park, IL 60064-3500 (US).

(81) Designated States: CA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: ENDOTHELIN ANTAGONISTS



(I)

(57) Abstract

A compound of formula (I) or a pharmaceutically acceptable salt thereof, as well as processes for and intermediates in the preparation thereof, and methods and compositions of antagonizing endothelin.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo			SE	Sweden
CH	Switzerland	KR	Republic of Korea	SI	Slovenia
CI	Côte d'Ivoire	KZ	Kazakhstan	SK	Slovakia
CM	Cameroon	LI	Liechtenstein	SN	Senegal
CN	China	LK	Sri Lanka	TD	Chad
CS	Czechoslovakia	LU	Luxembourg	TG	Togo
CZ	Czech Republic	LV	Latvia	TJ	Tajikistan
DE	Germany	MC	Monaco	TT	Trinidad and Tobago
DK	Denmark	MD	Republic of Moldova	UA	Ukraine
ES	Spain	MG	Madagascar	US	United States of America
FI	Finland	ML	Mali	UZ	Uzbekistan
FR	France	MN	Mongolia	VN	Viet Nam
GA	Gabon				

ENDOTHELIN ANTAGONISTS

This is a continuation-in-part of U.S. patent application Serial No. 126,822, filed September 24, 1993.

Technical Field

The present invention relates to compounds which are endothelin antagonists, processes for making such compounds, synthetic intermediates employed in these processes and methods and compositions for antagonizing endothelin.

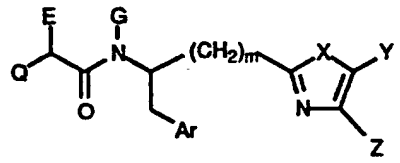
Background of the Invention

Endothelin (ET) is a 21 amino acid peptide that is produced by endothelial cells. ET is produced by enzymatic cleavage of a Trp-Val bond in the precursor peptide big endothelin (Big ET). This cleavage is caused by an endothelin converting enzyme (ECE). Endothelin has been shown to constrict arteries and veins, increase mean arterial blood pressure, decrease cardiac output, increase cardiac contractility in vitro, stimulate mitogenesis in vascular smooth muscle cells in vitro, contract non-vascular smooth muscle including guinea pig trachea, human urinary bladder strips and rat uterus in vitro, increase airway resistance in vivo, induce formation of gastric ulcers, stimulate release of atrial natriuretic factor in vitro and in vivo, increase plasma levels of vasopressin, aldosterone and catecholamines, inhibit release of renin in vitro and stimulate release of gonadotropins in vitro.

It has been shown that vasoconstriction is caused by binding of endothelin to its receptors on vascular smooth muscle (Nature 332 411 (1988), FEBS Letters 231 440 (1988) and Biochem. Biophys. Res. Commun. 154 868 (1988)). An agent which suppresses endothelin production or an agent which binds to endothelin or which inhibits the binding of endothelin to an endothelin receptor will produce beneficial effects in a variety of therapeutic areas. In fact, an anti-endothelin antibody has been shown, upon intrarenal infusion, to ameliorate the adverse effects of renal ischemia on renal vascular resistance and glomerular filtration rate (Kon, et al., J. Clin. Invest. 83 1762 (1989)). In addition, an anti-endothelin antibody attenuated the nephrotoxic effects of intravenously administered cyclosporin (Kon, et al., Kidney Int. 37 1487 (1990)) and attenuated infarct size in a coronary artery ligation-induced myocardial infarction model (Watanabe, et al., Nature 344 114 (1990)).

Disclosure of the Invention

In accordance with the present invention there are compounds of the formula (I):



(I)

wherein m is 0, 1 or 2;

X is $-N(R_2)-$, -O- or -S-, wherein R_2 is hydrogen, loweralkyl, arylalkyl or (heterocyclic)alkyl;

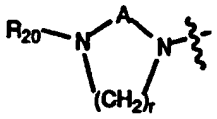
Q is (1) R_1-A-N(B)- wherein

A is $-C(O)-$ or $-S(O)_2-$;

R_1 is loweralkyl, cycloalkyl, cycloalkylalkyl, arylalkyl, aryl, alkoxy, arylalkoxy, cycloalkoxy, cycloalkylalkoxy,

aryloxy, alkylamino, cycloalkylamino, arylamino, cycloalkylalkylamino, arylalkylamino, dialkylamino, diarylamino, (alkyl)cycloalkylamino, (alkyl)arylamino, (alkyl)cycloalkylalkylamino, (alkyl)arylalkylamino, heterocyclic, (heterocyclic)alkyl, (heterocyclic)amino, spirocarbocyclic or spiroheterocyclic; and

B is hydrogen or loweralkyl; or



(2) wherein A is as defined above, R_{20} is loweralkyl, cycloalkyl, cycloalkylalkyl, arylalkyl, aryl, heterocyclic, (heterocyclic)alkyl, spirocarbocyclic or spiroheterocyclic, and r is 2 to 4;

E is loweralkyl optionally substituted with one, two or three substituents independently selected from cyano, halo, hydroxy, alkoxy, amino, alkylamino, dialkylamino, thioalkoxy and azido;

G is hydrogen or loweralkyl;

Ar is bicyclic aryl or bicyclic heteroaryl; and

Y and Z are independently selected from the group consisting of

(1) hydrogen;

(2) loweralkyl;

(3) loweralkyl substituted with one, two or three groups independently selected from cyano, hydroxy, alkoxy, amino, alkylamino, dialkylamino, azido, thioalkoxy, and halo;

(4) cycloalkyl;

(5) (cycloalkyl)alkyl;

(6) aryl;

(7) arylalkyl;

(8) a radical of the formula $-(CH_2)_n-C(O)-W$ wherein W is $-OR_{10}$ wherein R_{10} is hydrogen or a carboxy protecting group, amino, alkylamino, dialkylamino,

hydroxyamino, N-hydroxyl-N-alkylamino or a naturally occurring α-amino acid wherein the amino acid is bonded through the α-amino group;

(9) a radical of the formula $-(CH_2)_n-V$ wherein V is

(a) $-S(O)_2NHC(O)R_{16}$ wherein R_{16} is loweralkyl, haloalkyl, or phenyl,

(b) $-PO_3H_2$,

(c) -P(O)(OH)E wherein E is hydrogen, loweralkyl or arylalkyl,

(d) -CN,

(e) $-C(O)NHR_{17}$ wherein R_{17} is loweralkyl,

(f) alkylaminocarbonyl,

(g) dialkylaminocarbonyl,

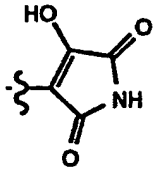
(h) tetrazolyl,

(i) hydroxy,

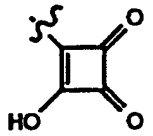
(j) alkoxy,

(k) sulfonamido,

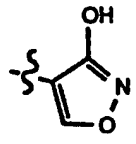
(l) $-C(O)NHS(O)_2R_{16}$ wherein R_{16} is defined as above,

(m) 

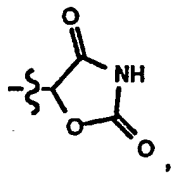
,

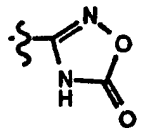
(n) 

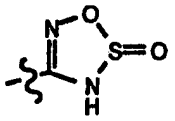
,

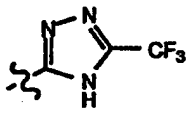
(o) 

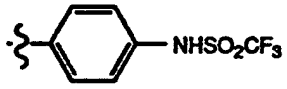
,

(p)  ,

(q)  ,

(r)  ,

(s)  , or

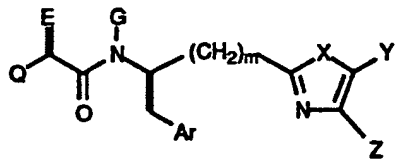
(t)  ; and

(10) $-(CH_2)_n-NHS(O)_2R_6$ wherein R_6 is loweralkyl or haloalkyl and wherein at each occurrence n as used above is independently selected from 0, 1 or 2;

with the proviso that at least one of Y or Z is a radical of the formula $-(CH_2)_n-C(O)-W$, $-(CH_2)_n-V$ or $-(CH_2)_n-NHS(O)_2R_6$ wherein n, W and R_6 are defined as above;

or a pharmaceutically acceptable salt thereof.

A preferred embodiment of the present invention is a compound of formula (II):



(II)

wherein Q, E, Ar, G, Ar, X, Y, Z and m are as defined above; or a pharmaceutically acceptable salt thereof.

A preferred embodiment of the invention is a compound of formula (I) or (II) wherein

Q is R_1-C(O)-N(B)-;

Y is

(1) hydrogen;

(2) loweralkyl;

(3) loweralkyl substituted with one, two or three substituents independently selected from the group consisting of cyano, hydroxy, alkoxy, amino, alkylamino, dialkylamino, thioalkoxy, and halo;

(4) cycloalkyl;

(5) (cycloalkyl)alkyl;

(6) aryl;

(7) arylalkyl or

(8) a radical of the formula -$(CH_2)_n$-C(O)-W wherein W is -OR_{10} wherein R_{10} is hydrogen or a carboxy protecting group;

Z is

(1) a radical of the formula $-(CH_2)_n-C(O)-W$ wherein W is $-OR_{10}$ wherein R_{10} is hydrogen or a carboxy protecting group, amino, alkylamino, dialkylamino, hydroxyamino, N-hydroxyl-N-alkylamino and a naturally occurring α-amino acid wherein the amino acid is bonded through the α-amino group;

(2) $-(CH_2)_n$-(tetrazolyl) or

(3) $-(CH_2)_n-NHS(O)_2R_6$ wherein R_6 is loweralkyl or haloalkyl and at each occurrence n as used above is independently selected from 0, 1 or 2; and

R_1, E, Ar, B, G, m and X are as defined above;

or a pharmaceutically acceptable salt thereof.

Another preferred embodiment of the present invention is a compound of formula (I) or (II) wherein

Q is $R_1-C(O)-N(B)-$;

Y is

(1) a radical of the formula $-(CH_2)_n-C(O)-W$ wherein W is $-OR_{10}$ wherein R_{10} is hydrogen or a carboxy protecting group, amino, alkylamino, dialkylamino, hydroxyamino, N-hydroxyl-N-alkylamino and a naturally occurring α-amino acid wherein the amino acid is bonded through the α-amino group;

(2) $-(CH_2)_n$-(tetrazolyl) or

(3) $-(CH_2)_n-NHS(O)_2R_6$ wherein R_6 is loweralkyl or haloalkyl;

Z is

(1) hydrogen;

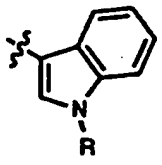
(2) loweralkyl;

(3) loweralkyl substituted with one, two or three substituents independently selected from the group consisting of cyano, hydroxy, alkoxy, amino, alkylamino, dialkylamino, thioalkoxy, and halo;

(4) cycloalkyl;
(5) (cycloalkyl)alkyl;
(6) aryl;
(7) arylalkyl or
(8) a radical of the formula $-(CH_2)_n-C(O)-W$ wherein W is $-OR_{10}$ wherein R_{10} is hydrogen or a carboxy protecting group;

wherein at each occurrence n as used above is independently selected from 0, 1 or 2 and R_1, E, Ar, B, G, m and X are as defined above; or a pharmaceutically acceptable salt thereof.

A more preferred embodiment of the present invention is a compound of formula (I) or (II)
wherein
Q is $R_1-C(O)-N(B)-$ wherein R_1 is loweralkyl, (alkyl)cycloalkylamino, cycloalkoxy, arylamino, (alkyl)arylamino, diarylamino, cycloalkyl, cycloalkylalkyl, arylalkyl, arylalkoxy, cycloalkylalkylamino, cycloalkylamino, alkoxy, arylalkylamino, dialkylamino, spiroheterocyclic or heterocyclic, and B is hydrogen or methyl;
E is isobutyl;
G is hydrogen;



Ar is wherein R is hydrogen or loweralkyl;
Y is hydrogen, arylalkyl, haloalkyl, loweralkyl, aryl or cycloalkyl;
Z is a radical of the formula $-(CH_2)_n-CO-W$, wherein W is $-OR_{10}$, wherein R_{10} is hydrogen or a carboxy protecting group, alkylamino, hydroxyamino or a naturally occurring α-amino acid wherein the amino acid is bonded through the α-amino group or $-(CH_2)_n-$(tetrazolyl) wherein n as used above is 0 or 1;
m is 0 or 1; and
X is $-N(R_2)-$, -O- or -S-, wherein R_2 is hydrogen or loweralkyl;

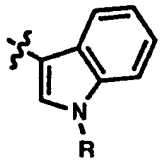
or a pharmaceutically acceptable salt thereof.

A yet more preferred embodiment is a compound of formula (I) or (II) wherein

Q is R_1-C(O)-N(B)- wherein R_1 is cycloalkylamino, arylamino, arylalkyl, spiroheterocyclic, heterocyclic, (alkyl)arylamino, cycloalkoxy, or (alkyl)cycloalkylamino and B is hydrogen or methyl;

E is isobutyl;

G is hydrogen;

Ar is  wherein R is hydrogen or methyl;

X is -NH- or -O- ;

m is 0;

Y is loweralkyl; and

Z is $-CO_2H$;

or a pharmaceutically acceptable salt thereof.

The present invention also relates to processes for preparing the compounds of formula (I) and (II) and to the synthetic intermediates employed in these processes.

The present invention also relates to a method of antagonizing endothelin in a mammal in need of such treatment, comprising administering to the mammal a therapeutically effective amount of a compound of formula (I) or (II).

The invention further relates to endothelin antagonizing compositions comprising a pharmaceutical carrier and a therapeutically effective amount of a compound of formula (I) or (II).

The compounds of the invention comprise two or more asymmetrically substituted carbon atoms. As a result, all possible stereoisomers, including racemic mixtures, mixtures of diastereomers, as well as single diastereomers of the compounds of the invention are included in the present invention. The terms "S" and "R" configuration are as defined by the IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry, Pure Appl. Chem. (1976) 45, 13 - 30.

The terms "Gly", "Trp", "Val" and "Leu" as used herein refer to glycine, tryptophan, valine and leucine, respectively. In general, the amino acid abbreviations used herein follow the IUPAC-IUB Joint Commission on Biochemical Nomenclature for amino acids and peptides (Eur. J. Biochem. 1984, 158, 9-31).

The term "naturally occuring amino acid" refers to an α-amino acid selected from the group consisting of alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, ornithine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine. The stereochemistry at the asymmetric center can be of the D- or L-configuration.

The term "N-protecting group" or "N-protected" as used herein refers to those groups intended to protect the N-terminus of an amino acid or peptide or to protect an amino group against undersirable reactions during synthetic procedures. Commonly used N-protecting groups are disclosed in Greene, "Protective Groups In Organic Synthesis," (John Wiley & Sons, New York (1981)), which is hereby incorporated by reference. N-protecting groups comprise acyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, phthalyl, o-nitrophenoxyacetyl, α-chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and the like; sulfonyl groups such as benzenesulfonyl, p-toluenesulfonyl and the like; carbamate forming groups such as benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl,

3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenylyl)-1-methylethoxycarbonyl, α,α-dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxycarbonyl, t-butyloxycarbonyl, diisopropylmethoxycarbonyl, isopropyloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2,-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxycarbonyl, fluorenyl-9-methoxycarbonyl, cyclopentyloxycarbonyl, adamantyloxycarbonyl, cyclohexyloxycarbonyl, phenylthiocarbonyl and the like; alkyl groups such as benzyl, triphenylmethyl, benzyloxymethyl and the like; and silyl groups such as trimethylsilyl and the like. Preferred N-protecting groups are formyl, acetyl, benzoyl, pivaloyl, t-butylacetyl, phenylsulfonyl, benzyl, t-butyloxycarbonyl (Boc) and benzyloxycarbonyl (Cbz).

The term "carboxy protecting group" as used herein refers to a carboxylic acid protecting ester group employed to block or protect the carboxylic acid functionality while the reactions involving other functional sites of the compound are carried out. Carboxy-protecting groups are disclosed in Greene, "Protective Groups in Organic Synthesis" pp. 152-186 (1981), which is hereby incorporated herein by reference. In addition, a carboxy-protecting group can be used as a prodrug whereby the carboxy-protecting group can be readily cleaved *in vivo* , for example by enzymatic hydrolysis, to release the biologically active parent. T. Higuchi and V. Stella provide a thorough discussion of the prodrug concept in "Pro-drugs as Novel Delivery Systems", Vol 14 of the A.C.S. Symposium Series, American Chemical Society (1975), which is hereby incorporated herein by reference. Such carboxy-protecting groups are well known to those skilled in the art, having been extensively used in the protection of carboxyl groups in the penicillin and cephalosporin fields, as described in U.S. Pat. No. 3,840,556 and 3,719,667, the disclosures of which are hereby incorporated herein by reference. Examples of esters useful as prodrugs for compounds

containing carboxyl groups can be found on pages 14-21 of "Bioreversible Carriers in Drug Design: Theory and Application", edited by E.B. Roche, Pergamon Press, New York (1987), which is hereby incorporated herein by reference. Representative carboxy-protecting groups are C_1 to C_8 loweralkyl (e.g., methyl, ethyl or tertiary butyl and the like); benzyl and substituted derivatives thereof such as alkoxybenzyl or nitrobenzyl groups and the like; dialkylaminoalkyl (e.g., dimethylaminoethyl and the like); alkanoyloxyalkyl groups such as pivaloyloxymethyl or propionyloxymethyl and the like; aroyloxyalkyl, such as benzoyloxyethyl and the like; alkoxycarbonylalkyl, such as methoxycarbonylmethyl, cyclohexyloxycarbonylmethyl and the like; alkoxycarbonyloxyalkyl, such as t-buyloxycarbonyloxymethyl and the like; alkoxycarbonylaminoalkyl, such as t-butyloxycarbonylaminomethyl and the like; alkylaminocarbonylaminoalkyl, such as methylaminocarbonylaminomethyl and the like; alkanoylaminoalkyl, such as acetylaminomethyl and the like; heterocycliccarbonyloxyalkyl, such as 4-methylpiperazinylcarbonyloxymethyl and the like; dialkylaminocarbonylalkyl, such as dimethylaminocarbonylmethyl and the like; (5-(loweralkyl)-2-oxo-1,3-dioxolen-4-yl)alkyl, such as (5-t-butyl-2-oxo-1,3-dioxolen-4-yl)methyl and the like; and (5-phenyl-2-oxo-1,3-dioxolen-4-yl)alkyl, such as (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methyl and the like.

The terms "loweralkyl" or "alkyl" as used herein refer to straight or branched chain alkyl radicals containing from 1 to 10 carbon atoms including, but not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl, n-pentyl, 1-methylbutyl, 2,2-dimethylbutyl, 2-methylpentyl, 2,2-dimethylpropyl, n-hexyl and the like.

The term "alkylamino" as used herein refers to $R_{51}NH$- wherein R_{51} is a loweralkyl group, for example, ethylamino, butylamino, and the like.

The term "alkylaminocarbonyl" as used herein refers to an alkylamino group, as previously defined, appended to the parent molecular moiety through a carbonyl (-C(O)-) linkage. Examples of

alkylaminocarbonyl include methylaminocarbonyl, ethylaminocarbonyl, isopropylaminocarbonyl and the like.

The term "alkylaminocarbonylaminoalkyl" as used herein refers to R_{90}-C(O)-NH-R_{91}- wherein R_{90} is an alkylamino group and R_{91} is an alkylene group. Examples of alkylaminocarbonylaminoalkyl include methylaminocarbonylaminomethyl, ethylaminocarbonylaminomethyl and the like.

The term "dialkylamino" as used herein refers to $R_{56}R_{57}N$- wherein R_{56} and R_{57} are independently selected from loweralkyl, for example diethylamino, methyl propylamino, and the like.

The term "dialkylaminoalkyl" as used herein refers to $R_{71}R_{72}N$-R_{73}- wherein R_{71} and R_{72} are independently selected from loweralkyl and R_{73} is an alkylene group. Examples of dialkylaminoalkyl include dimethylaminomethyl, dimethylaminoethyl, N-ethyl-N-methylaminomethyl, and the like.

The term "dialkylaminocarbonyl" as used herein refers to a dialkylamino group, as previously defined, appended to the parent molecular moiety through a carbonyl (-C(O)-) linkage. Examples of dialkylaminocarbonyl include dimethylaminocarbonyl, diethylaminocarbonyl and the like.

The term "dialkylaminocarbonylalkyl" as used herein refers to R_{100}-C(O)-R_{101}- wherein R_{100} is a dialkylamino group and R_{101} is an alkylene group, for example, dimethylaminocarbonylmethyl and the like.

The term "(alkyl)arylamino" as used herein refers to $R_{60}R_{61}N$- wherein R_{60} is an aryl group and R_{61} is a loweralkyl group.

The term "(alkyl)arylalkylamino" as used herein refers to $R_{64}R_{65}N$- wherein R_{64} is an arylalkyl group and R_{65} is a loweralkyl group.

The term "(alkyl)cycloalkylamino" as used herein refers to $R_{58}R_{59}N$- wherein R_{58} is a cycloalkyl group and R_{59} is a loweralkyl group.

The term "(alkyl)cycloalkylalkylamino" as used herein refers to $R_{62}R_{63}N$- wherein R_{62} is an cycloalkylalkyl group and R_{63} is a loweralkyl group.

The term "alkanoylaminoalkyl" as used herein refers to R_{93}-NH-R_{94}- wherein R_{93} is an alkanoyl group and R_{94} is an alkylene group. Examples of alkanoylaminoalkyl include acetylaminomethyl, acetylaminoethyl and the like.

The term "alkanoyloxyalkyl" as used herein refers to R_{74}-O-R_{75}- wherein R_{74} is an alkanoyl group and R_{75} is an alkylene group. Examples of alkanoyloxyalkyl include acetoxymethyl, acetoxyethyl and the like.

The term "alkoxy" as used herein refers to $R_{41}O$- wherein R_{41} is a loweralkyl group, as defined above. Examples of alkoxy include, but are not limited to, ethoxy, tert-butoxy, and the like.

The term "alkoxyalkoxy" as used herein refers to $R_{80}O$-$R_{81}O$- wherein R_{80} is loweralkyl as defined above and R_{81} is alkylene wherein alkylene is $-(CH_2)_{n'}-$ wherein n' is an integer from 1 to 6. Representative examples of alkoxyalkoxy groups include methoxymethoxy, ethoxymethoxy, t-butoxymethoxy and the like.

The term "alkoxycarbonyl" as used herein refers to an alkoxyl group as previously defined appended to the parent molecular moiety through a carbonyl group. Examples of alkoxycarbonyl include methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl and the like.

The term "alkoxycarbonylaminoalkyl" as used herein refers to R_{88}-C(O)-NH-R_{89}- wherein R_{88} is an alkoxy group and R_{89} is an alkylene group.

The term "alkoxycarbonylalkyl" as used herein refers to R_{84}-C(O)-R_{85}- wherein R_{84} is an alkoxy group and R_{85} is an alkylene group. Examples of alkoxycarbonylalkyl include methoxycarbonylmethyl, methoxcarbonylethyl, ethoxycarbonylmethyl and the like.

The term "alkoxycarbonyloxyalkyl" as used herein refers to R_{86}-C(O)-O-R_{87}- wherein R_{86} is an alkoxy group and R_{87} is an alkylene group. Examples of alkoxycarbonyloxyalkyl include tert-butyloxycarbonylmethyl, tert-butyloxycarbonylethyl, and the like.

The term "alkylene" denotes a divalent group derived from a straight or branched chain saturated hydrocarbon having from 1 to 10 carbon atoms by the removal of two hydrogen atoms, for example methylene, 1,2-ethylene, 1,1-ethylene, 1,3-propylene, 2,2-dimethylpropylene, and the like.

The term "aryl" as used herein refers to a mono- or bicyclic carbocyclic ring system having one or more aromatic rings including, but not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl, indenyl and the like. The term "bicyclic aryl" as used herein includes naphthyl, tetrahydronaphthyl, indanyl, indenyl and the like. Aryl groups (including bicyclic aryl groups) can be unsubstituted or substituted with one, two or three substituents independently selected from loweralkyl, haloalkyl, alkoxy, thioalkoxy, amino, alkylamino, dialkylamino, hydroxy, halo, mercapto, nitro, carboxaldehyde, carboxy, alkoxycarbonyl and carboxamide. In addition, substituted aryl groups include tetrafluorophenyl and pentafluorophenyl.

The term "arylalkoxy" as used herein refers to $R_{42}O$- wherein R_{42} is an arylalkyl group, for example, benzyloxy, and the like.

The term "arylalkyl" as used herein refers to an aryl group as previously defined, appended to a loweralkyl radical, for example, benzyl and the like.

The term "arylalkylamino" as used herein refers to $R_{55}NH$- wherein R_{55} is an arylalkyl group, for example benzylamino and the like.

The term "arylamino" as used herein refers to $R_{53}NH$- wherein R_{53} is an aryl group, for example, anilino, and the like.

The term "aryloxy" as used herein refers to $R_{45}O$- wherein R_{45} is an aryl group, for example, phenoxy, and the like.

The term "aroyloxyalkyl" as used herein refers to R_{82}-C(O)-O-R_{83}- wherein R_{82} is an aryl group and R_{83} is an alkylene group. Examples of aroyloxyalkyl include benzoyloxymethyl, benzoyloxyethyl and the like.

The term "cycloalkyl" as used herein refers to an aliphatic ring system having 3 to 10 carbon atoms and 1 to 3 rings including, but not limited to, cyclopropyl, cyclopentyl, cyclohexyl, norbornyl, adamantyl, and the like. Cycloalkyl groups can be unsubstituted or substituted with one, two or three substituents independently selected from loweralkyl, haloalkyl, alkoxy, thioalkoxy, amino, alkylamino, dialkylamino, hydroxy, halo, mercapto, nitro, carboxaldehyde, carboxy, alkoxycarbonyl and carboxamide.

The term "cycloalkylalkyl" as used herein refers to a cycloalkyl group appended to a loweralkyl radical, including but not limited to cyclohexylmethyl.

The term "cycloalkoxy" as used herein refers to $R_{43}O$- wherein R_{43} is a cycloalkyl group, for example, cyclohexyloxy, and the like.

The term "cycloalkylalkoxy" as used herein refers to $R_{44}O$- wherein R_{44} is a cycloalkylalkyl group, for example, cyclohexylmethoxy, and the like.

The term "cycloalkylamino" as used herein refers to $R_{52}NH$- wherein R_{52} is a cycloalkyl group, for example, cyclohexylamino, and the like.

The term "cycloalkylalkylamino" as used herein refers to $R_{54}NH$- wherein R_{54} is a cycloalkylalkyl group, for example, cyclohexylmethylamino, and the like.

The term "diarylamino" as used herein refers to $R_{30}R_{31}N$- wherein R_{30} and R_{31} are independently selected from aryl as defined above.

The term "halogen" or "halo" as used herein refers to I, Br, Cl or F.

The term "haloalkyl" as used herein refers to a lower alkyl radical, as defined above, bearing at least one halogen substituent, for example, chloromethyl, fluoroethyl or trifluoromethyl and the like.

The terms "heterocyclic ring" or "heterocyclic" or "heterocycle" as used herein refers to any 3- or 4-membered ring containing a heteroatom selected from oxygen, nitrogen and sulfur; or a 5-, 6- or 7-membered ring containing one, two or three nitrogen atoms; one nitrogen and one sulfur atom; or one nitrogen and one oxygen atom. The 5-membered ring has 0-2 double bonds and the 6- and 7-membered ring have 0-3 double bonds. The nitrogen heteroatoms can be optionally quaternized. The term "heterocyclic" also includes bicyclic groups in which any of the above heterocyclic rings is fused to a benzene ring or a cyclohexane ring or another heterocyclic ring (for example, indolyl, quinolyl, isoquinolyl, tetrahydroquinolyl, decahydroquinolyl, benzofuryl or benzothienyl, imidazopyridyl, pyrrolopyridyl and the like). The term "heterocyclic" also includes tricyclic groups in which any of the above heterocyclic rings is fused to two benzene rings or two cyclohexane rings or two other heterocyclic rings (for example, carbazolyl, iminodibenzyl and the like). Heterocyclics include: azetidinyl, benzimidazolyl, 1,4-benzodioxanyl, 1,3-benzodioxolyl, benzoxazolyl, benzothiazolyl, benzothienyl, carbazolyl, dihydropyranyl, dihydrofuranyl, dioxanyl, dioxolanyl, furyl, homopiperidinyl, imidazolyl, imidazolinyl, imidazolidinyl, imidazopyridyl, iminodibenzyl, indolinyl, indolyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, isoxazolidinyl, isoxazolyl, morpholinyl, naphthyridinyl, oxazolidinyl, oxazolyl, piperazinyl, piperidinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolindinylpyridyl, pyrrolinyl, pyrrolopyridyl, pyrrolyl, quinolinyl, tetrahydrofuranyl, tetrahydropyranyl, thiazolidinyl, thiazolyl, and thienyl.

Heterocyclics can be unsubstituted or monosubstituted or disubstituted with substituents independently selected from hydroxy, halo, oxo (=O), alkylimino ($R^*N=$ wherein R^* is a loweralkyl group), amino, alkylamino, dialkylamino, alkoxy, alkoxyalkoxy, haloalkyl, cycloalkyl, aryl, arylalkyl, -COOH, $-SO_3H$ and loweralkyl. In addition, nitrogen containing heterocycles can be N-protected.

The term "(heterocyclic)alkyl" as used herein refers to a heterocyclic group as defined above appended to a loweralkyl radical as defined above.

The term "(heterocyclic)amino" as used herein refers to $R_{35}NH$- wherein R_{35} is a heterocyclic group. Examples of (heterocyclic)amino include 4-pyridylamino, 3-pyridylamino, 2-pyridylamino and the like.

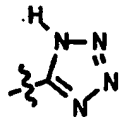
The term "heterocycliccarbonyloxyalkyl" as used herein refers to R_{96}-C(O)-O-R_{97}- wherein R_{96} is a heterocyclic group and R_{97} is an alkylene group, for example, 4-methylpiperazinylcarbonyloxymethyl and the like.

The term "bicyclic heteroaryl" as used herein refers to a monocyclic heterocycle as defined above to which is fused a benzene ring, a cyclohexane ring or a monocyclic heterocycle as defined above, with the proviso that at least one of the rings of the bicyclic group is aromatic. Examples of bicyclic heteroaryl include indolyl, indolinyl, quinolyl, isoquinolyl, tetrahydroquinolyl, benzofuryl, benzothienyl and the like. Bicyclic heteroaryl groups can be unsubstituted or monosubstituted or disubstituted with substituents independently selected from hydroxy, halo, oxo (=O), alkylimino (R*N= wherein R* is a loweralkyl group), amino, alkylamino, dialkylamino, alkoxy, alkoxyalkoxy, haloalkyl, cycloalkyl, aryl, arylalkyl, -CHO, -COOH, -SO_3H and loweralkyl. In addition, nitrogen containing heterocycles can be N-protected.

The term "spirocarbocyclic" or "spirocarbocycle" as used herein refers to a bicyclic hydrocarbon in which the ring pair has just one carbon-atom in common, which is designated the "spiro atom". Spirocarbocyclic compounds can be unsubstituted or substituted with one, two or three groups selected from loweralkyl, hydroxy, alkoxy, halo, haloalkyl and carboxy. Examples of spirocarbocycles include spiropentane, spirohexane, spiro[4.4]nonane and the like.

The term "spiroheterocyclic" or "spiroheterocycle" as used herein refers to a bicyclic spirocyclic ring system containing carbon atoms and at least one heteroatom selected from oxygen, nitrogen and sulfur. Examples of spiroheterocycles include 1-oxa-4-azaspiro[5.4]decane, 1,4-diaza[5.4]decane and the like. Spiroheterocyclics can be substituted in the same way as defined above for heterocyclics.

The term "tetrazolyl" as used herein refers to a radical of the formula



or a tautomer thereof.

The term "thioalkoxy" as used herein refers to $R_{70}S$- wherein R_{70} is loweralkyl. Examples of thioalkoxy include, but are not limited to, methylthio, ethylthio and the like.

Representative compounds of the invention include:

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid;
2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid;
2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-phenyl-imidazole-4-carboxylic acid;
2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-benzyl-imidazole-4-carboxylic acid;
2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-ethyl-imidazole-4-carboxylic acid;
2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-propyl-imidazole-4-carboxylic acid;
2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-isopropyl-imidazole-4-carboxylic acid;

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-cyclopropyl-imidazole-4-carboxylic acid;
2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid ethyl ester;
2-{(1R)-1-[N-(N-Homopiperidin-1-ylcarbonyl-N-methyl-Leucyl)-amino]-2-(indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid;
1,5-Dimethyl-2-{(1R)-1-[N-(homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-imidazole-4-carboxylic acid;
1-Benzyl-2-{(1R)-1-[N-(homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid;
2-{(1R)-1-[N-(Cyclohexylaminocarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid;
2-{(1R)-1-[N-(4-Methoxymethoxypiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid;
2-{(1R)-1-[N-(Homopiperidin-1-ylsulfonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid;
2-{(1R)-1-[N-Boc-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid;
2-{(1R)-1-[N-(Benzylaminocarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid;
2-{(1R)-1-[N-(Phenylacetyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid;
2-{(1R)-1-[N-(1-Naphthylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid;
2-{(1R)-1-[N-(Cyclohexylacetyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid;
2-{(1R)-1-[N-(Cycloheptylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid;
2-{(1R)-1-[N-(Norborn-2-ylacetyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid;
2-{(1R)-1-[N-(4-Methoxyphenylacetyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid;

2-{(1R)-1-[N-(3,3-Dimethylbutyryl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid;

2-{(1R)-1-[N-(2-Propylvaleryl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid;

2-{(1R)-1-[N-(3-Pyridylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid;

2-{(1R)-1-[N-(Cyclohexylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-imidazole-4-carboxylic acid;

2-{(1R)-1-[N-(*endo*-2-Norbornylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid;

2-{(1R)-1-[N-(*exo*-2-Norbornylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid;

2-{(1R)-1-[N-(*trans*-4-Hydroxycyclohexylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid;

2-{(1R)-1-[N-(2-Methylcyclohexylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-imidazole-4-carboxylic acid;

2-{(1R)-1-[N-(3-Methylcyclohexylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-imidazole-4-carboxylic acid;

2-{(1R)-1-[N-(4-Methylcyclohexylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-imidazole-4-carboxylic acid;

2-{(1R)-1-[(N-Cyclopentylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-imidazole-4-carboxylic acid;

2-{(1R)-1-[(N-Cycloheptylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-imidazole-4-carboxylic acid;

2-{(1R)-1-[N-(N-Cyclohexyl-N-methylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-imidazole-4-carboxylic acid;

2-{(1R)-1-[(N-Cyclohexylaminocarbonyl)-Leucyl-amino]-2-(1-ethyl-indol-3-yl)ethyl]-5-methyl-imidazole-4-carboxylic acid;

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-imidazole-4,5-dicarboxylic acid;

2-{2R-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-3-(indol-3-yl)propyl}-5-methyl-imidazole-4-carboxylic acid;

2-{(1R)-1-[N-(N-(Homopiperidin-1-ylcarbonyl)-Leucyl)-N-methylamino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid;

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-imidazole-4-carboxylic acid;

2-{(1R)-1-[N-(Cyclohexyloxycarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid;

2-{(1R)-1-[N-(Phenylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid;

2-{(1R)-1-[N-(N-Cyclohexylaminocarbonyl-N-methyl-Leucyl)-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-imidazole-4-carboxylic acid;

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-thiazole-4-carboxylic acid;

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-ethyl-thiazole-4-carboxylic acid;

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-propyl-thiazole-4-carboxylic acid;

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-trifluoromethyl-thiazole-4-carboxylic acid;

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-isopropyl-thiazole-4-carboxylic acid;

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-cyclopropyl-thiazole-4-carboxylic acid;

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-phenyl-thiazole-4-carboxylic acid;

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-benzyl-thiazole-4-carboxylic acid;

2-{2R-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-3-(indol-3-yl)propyl}-5-methyl-thiazole-4-carboxylic acid;

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-thiazole-4-carboxylic acid;

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-4-trifluoromethyl-thiazole-5-carboxylic acid;

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-thiazole-5-carboxylic acid;

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-[(Cyclohexylaminocarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-[(4-Methoxymethoxypiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-[N-(Homopiperidin-1-ylsulfonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-phenyl-oxazole-4-carboxylic acid;

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-benzyl-oxazole-4-carboxylic acid;

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-ethyl-oxazole-4-carboxylic acid;

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-propyl-oxazole-4-carboxylic acid;

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-cyclopropyl-oxazole-4-carboxylic acid;

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-isopropyl-oxazole-4-carboxylic acid;

2-{(1R)-1-[N-(N-Homopiperidin-1-ylcarbonyl-N-methyl-Leucyl)-amino]-2-(indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid ethyl ester;

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-oxazole-4-(N-hydroxy)carboxamide;

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-oxazole-4-(N-methyl)carboxamide;

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-oxazole-4-(N-carboxymethyl)carboxamide;
2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-oxazole-4-acetic acid;
2-{2R-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-3-(indol-3-yl)propyl}-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-[(N-Boc-Leucyl)-amino]-2-(indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-[N-Phenylacetyl-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-[N-(Benzylaminocarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-[N-(Benzenesulfonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-[N-(N,N-Diethylaminocarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-[N-(Cyclohexylacetyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-[N-(2-Propylvaleryl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-[N-(3,3-Dimethylbutyryl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-[N-(Cycloheptylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-[N-(Norborn-2-ylacetyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-[N-(4-Methoxyphenylacetyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-[(N-Cbz-Leucyl)-amino]-2-(indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-4-trifluoromethyl-oxazole-5-carboxylic acid;
2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-oxazole-4-carboxylic acid;
2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-oxazole-5-carboxylic acid;
2-{(1R)-1-[N-(*exo*-2-Norbornylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-[N-(*endo*-2-Norbornylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-[N-(N-Cyclohexylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-[N-(N-Methyl-N-cyclohexylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-[N-(N-Ethyl-N-cyclohexylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-[N-(N-Propyl-N-cyclohexylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-[N-(*trans*-4-Hydroxycyclohexylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-[N-(2-Methylcyclohexylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-[N-(3-Methylcyclohexylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-[N-(4-Methylcyclohexylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-[N-(Cyclopentylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-[N-(Cycloheptylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-[N-(1-Piperidinylcarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-[N-(4-Morpholinylcarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-[N-(1-Carbomethoxycyclohexylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-[N-(1,2,3,4-Tetrahydronaphthyl-1-aminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-[N-(1-Adamantylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-[N-(2-Adamantylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-[N-(1-oxa-4-azaspiro[5.4]decane-4-carbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-[N-(1-Indolinylcarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-[N-(Decahydroquinolin-1-ylcarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-[N-(1,2,3,4-Tetrahydroquinolin-1-ylcarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-[N-(N-Cyclohexylaminocarbonyl)-Leucyl-amino]-2-(1-ethyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-[N-(N-Cyclohexylaminocarbonyl)-Leucyl-amino]-2-(1-propyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-[N-(N-Methyl-N-phenylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-[N-(2-Pyridylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid; (Ex 115)
2-{(1R)-1-[N-(3-Pyridylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-[N-(Pentafluorophenylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-[N-(2-Hydroxyphenylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-[N-(Cyclohexyloxycarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-[N-(N-Cyclohexyl-N-methylaminocarbonyl)-Cyclohexylalanyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-[N-(N-(Homopiperidin-1-ylcarbonyl)-Leucyl)-N-methylamino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-[N-(N-Cyclohexylaminocarbonyl-N-methyl-Leucyl)-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-[(2R)-2-(3-Cyclohexyl-2-imidazolidone-1-yl)-4-methylvaleramido]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-[N-(1-Methylcyclohexylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-[N-(Phenylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-[N-(3-Fluorophenylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-[N-(N,N-Diphenylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-[N-(2-Fluorophenylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-[N-(4-Fluorophenylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-[N-(N-Carbazolylcarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-[N-(7-Azaindolin-1-ylcarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-[N-(7-Azaindole-1-carbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-[N-(Indole-1-carbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid; and

2-{(1R)-1-[N-(Indole-3-carbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid;

or a pharmaceutically acceptable salt thereof.

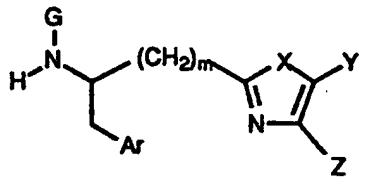
Preferred compounds are selected from the group consisting of:

2-{(1R)-1-(N-(Cyclohexylaminocarbonyl)-Leucyl-amino)-2-(indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid;
2-{(1R)-1-(N-(Cyclohexylaminocarbonyl)-Leucyl-amino)-2-(1-methyl-indol-3-yl)ethyl)-5-methyl-imidazole-4-carboxylic acid;
2-{(1R)-1-(N-(*endo*-2-Norbornylaminocarbonyl)-Leucyl-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid;
2-{(1R)-1-(N-(*exo*-2-Norbornylaminocarbonyl)-Leucyl-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid;
2-{(1R)-1-((N-Cyclopentylaminocarbonyl)-Leucyl-amino)-2-(1-methyl-indol-3-yl)ethyl)-5-methyl-imidazole-4-carboxylic acid;
2-{(1R)-1-(N-(Phenylaminocarbonyl)-Leucyl-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid;
2-{(1R)-1-[N-(N-Cyclohexylaminocarbonyl-N-methyl-Leucyl)-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-imidazole-4-carboxylic acid;
2-{(1R)-1-(N-(4-Methoxyphenylacetyl)-Leucyl-amino)-2-(indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-(N-(1-oxa-4-azaspiro(5.4)decane-4-carbonyl)-Leucyl-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-(N-(1-Indolinylcarbonyl)-Leucyl-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-(N-(Decahydroquinolin-1-ylcarbonyl)-Leucyl-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-(N-(1,2,3,4-Tetrahydroquinolin-1-ylcarbonyl)-Leucyl-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-(N-(N-Methyl-N-phenylaminocarbonyl)-Leucyl-amino)-2-(1-methyl-indol-3-yl)ethyl)-5-methyl-oxazole-4-carboxylic acid;

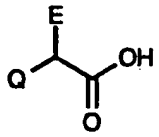
2-{(1R)-1-(N-(2-Hydroxyphenylaminocarbonyl)-Leucyl-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-(N-(Cyclohexyloxycarbonyl)-Leucyl-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-(N-(N-Cyclohexylaminocarbonyl-N-methyl-Leucyl)-amino)-2-(1-methyl-indol-3-yl)ethyl)-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-(N-(Phenylaminocarbonyl)-Leucyl-amino)-2-(1-methyl-indol-3-yl)ethyl)-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-(N-(3-Fluorophenylaminocarbonyl)-Leucyl-amino)-2-(1-methyl-indol-3-yl)ethyl)-5-methyl-oxazole-4-carboxylic acid; and
2-{(1R)-1-(N-(2-Fluorophenylaminocarbonyl)-Leucyl-amino)-2-(1-methyl-indol-3-yl)ethyl)-5-methyl-oxazole-4-carboxylic acid;

or a pharmaceutically acceptable salt thereof.

One process for preparing the compounds of the invention comprises reacting a compound of the formula:



wherein Ar, G, X, Y, Z and m are as defined above with a compound of the formula:



or an activated derivative thereof,
wherein Q and E are as defined above.

Additional processes for preparing the compounds of the invention are described below.

Methods for preparing the compounds of the invention are shown in Schemes I-V. The stereochemistry shown in the schemes is that of the preferred compounds of the invention. Compounds having other stereochemistry than that shown in the schemes can be obtained by starting with amino acids of opposite stereochemistry. In the following Schemes, X is -N(R_2)-, -O- or -S-, wherein R_2 is hydrogen, loweralkyl, arylalkyl or (heterocyclic)alkyl; and Y is hydrogen; loweralkyl; loweralkyl substituted with one, two or three groups independently selected from cyano, hydroxy, alkoxy, amino, alkylamino, dialkylamino, azido, thioalkoxy, and halo; cycloalkyl; (cycloalkyl)alkyl; aryl; or arylalkyl.

The synthesis of one series of heterocycle containing peptides (where m and n are 0) is shown in Scheme I. The anion of carboxy protected N-(diphenylmethylene)glycine (P" is a carboxy protecting group, for example methyl, ethyl or benzyl) (1) is formed using a non-nucleophilic base (for example, lithium hexamethyldisilazide), and the anion is acylated with the appropriate acid chloride (for example, when Y is methyl, the acid chloride is acetyl chloride) to give upon acid workup the acylated glycine 2 as its ammonium salt. The acylated glycine is coupled with an appropriately protected activated amino acid residue (P* is an nitrogen protecting group, Ar is bicyclic aryl or bicyclic heteroaryl and A* is an amino acid activating group, for example, chloride, fluoroide or mixed anhydride) to give 3. The heterocyclic ring is prepared using the appropriate reagents (for example, DBU, carbon tetrachloride and triphenylphosphine to prepare an oxazole; ammonium acetate to prepare an imidazole; and Lawesson's reagent to prepare a thiazole) to give compound 4. A similar route for the synthesis of heterocyclic dipeptide mimics has been described by Gordon, et al., Tetrahedron Lett. 34(12) 1901 (1993). This intermediate is either elaborated in a stepwise manner (Method A) or in a convergent manner (Method B) to give the final product (6). In Method A, the nitrogen protecting group is removed and the residue is coupled with a nitrogen-

protected amino acid or an activated ester derivative thereof (P is an nitrogen protecting group) to give compound 5. The nitrogen protecting group (P) is removed and the residue is terminally acylated. Removal of the carboxy protecting group (for example, hydrolysis of an alkyl ester or hydrogenolysis of a benzyl ester) provides the final product. The carboxy protecting group of the nitrogen protected intermediate 5 may also be removed (for example, hydrolysis of an alkyl ester or hydrogenolysis of a benzyl ester) (Method C) to give products where R_1-A- is an nitrogen protecting group (for example, when P is Boc, then the N-terminal group is a carbamate). Alternatively in Method B, the heterocyclic intermediate is nitrogen deprotected, coupled with a fully elaborated amino acid (R_1-C(O)-NH-CH(E)-CO_2H) residue or an activated ester derivative thereof and then the carboxy protecting group is removed (for example, hydrolysis of an alkyl ester or hydrogenolysis of a benzyl ester) to give the final product 6.

Activated ester derivatives of carboxylic acids include acid halides such as acid chlorides, and activated esters including, but not limited to, formic and acetic acid derived anhydrides, anhydrides derived from alkoxycarbonyl halides such as isobutyloxycarbonylchloride and the like, N-hydroxysuccinimide derived esters, N-hydroxyphthalimide derived esters, N-hydroxybenzotriazole derived esters, N-hydroxy-5-norbornene-2,3-dicarboxamide derived esters, 2,4,5-trichlorophenol derived esters and the like.

The synthesis of heterocycle containing peptides where m and n are not zero is shown in Scheme II. In the case where m is 1, the N-protected bicyclic aryl or bicyclic heteroaryl amino acid (P* is an nitrogen protecting group and Ar is bicyclic aryl or bicyclic heteroaryl) is homologated (for example, by activating the carboxy terminus, treating with diazomethane and then rearranging the resultant diazoketone) to give the N-protected "homo" amino acid 8. Treatment of 8 with the acylated glycine 2 (where P" is a carboxy protecting group, for example an alkyl or benzyl ester) described in Scheme I gives intermediate 9, which is cyclized by the procedures described in Scheme I to give

heterocycle 10. Compound 10 is further elaborated by the procedures described in Scheme I to give 10a.

The case where n is 1 is also described in Scheme II. In this case, heterocyclic intermediate 4 (P* is an nitrogen protecting group, P" is a carboxy protecting group and Ar is bicyclic aryl or bicyclic heteroaryl) is carboxy deprotected (for example, hydrolysis of an alkyl ester or hydrogenolysis of a benzyl ester) to give the heterocycle carboxylic acid 11. Activation of compound 11 (for example, by formation of the acid chloride), treatment with diazomethane, and rearrangement of the resultant diazoketone gives the acetic acid compound 12. Compound 12 can be elaborated to 12a as described in Scheme I. For the case where both m and n are 1, one would homologate the bicyclic aryl or heteroaryl amino acid as described in the first part of Scheme II and then also homologate the heterocyclic carboxylic acid by the procedure described in the second part of Scheme II. In the case where one desires m and/or n to be 2, one repeats the homologation reaction once again.

Another approach is shown in Scheme III; this scheme also shows the preparation of compounds wherein the positions of the nitrogen atom and X in the 5-membered heterocycle are reversed. Condensation of an amide 13 (X is O), thioamide 13 (X is S), or amidine 13 (X is NH), where Ar is bicyclic aryl or bicyclic heteroaryl and P* is an nitrogen protecting group, with α-halocarbonyl compound 13a (P" is a carboxy protecting group), followed by dehydration of the resultant aminol, provides compound 14. Condensation of 13 with α-halocarbonyl compound 13b (P" is a carboxy protecting group), followed by dehydration of the resulting aminol, provides compound 15. Deprotection of 14 or 15, coupling with an amino-terminal fragment, and carboxy deprotection, as described in Scheme I (Method A, B, or C), gives the final product, 14a or 15a, respectively.

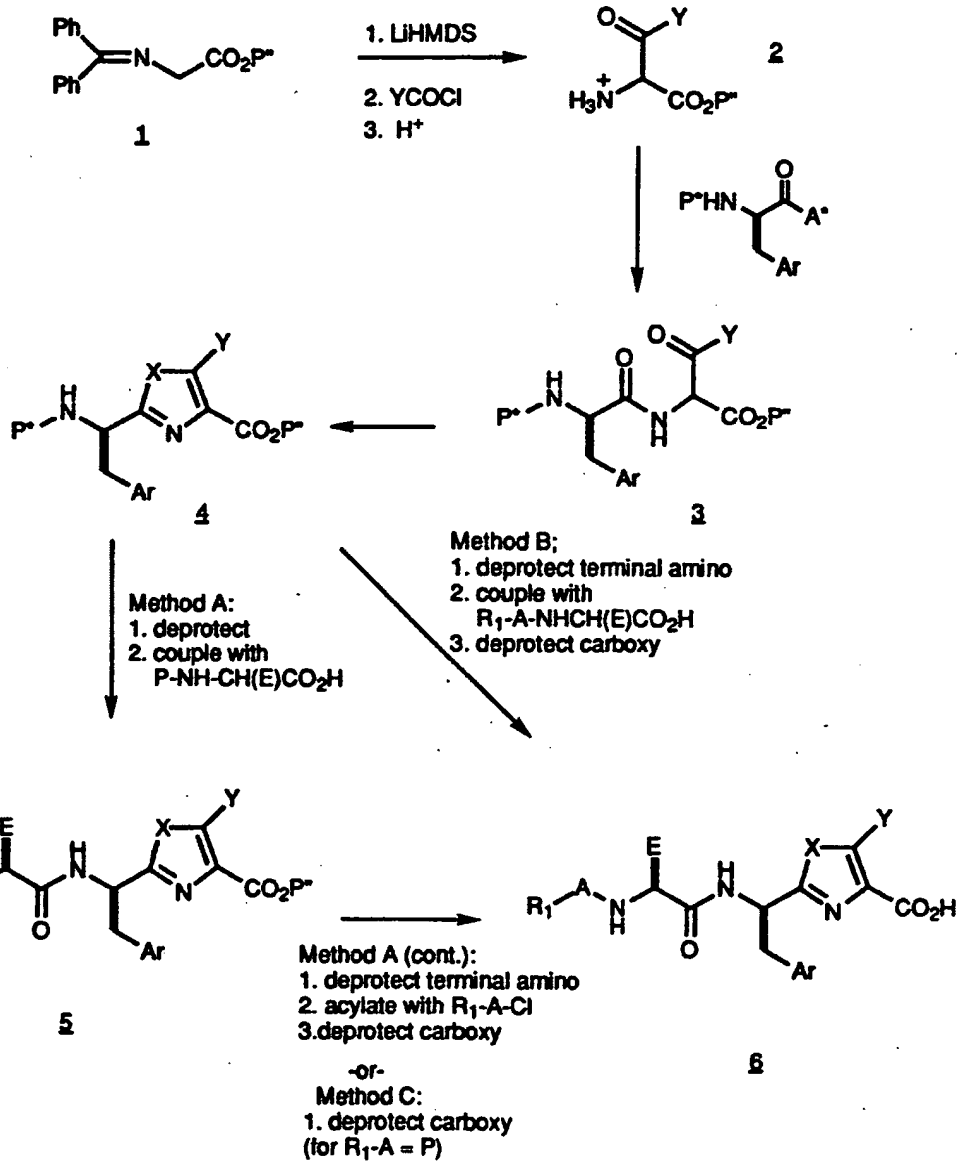
A preferred embodiment is shown in Scheme IV. The anion of N-(diphenylmethylene)glycine benzyl ester is formed using lithium hexamethyldisilazide and then is acylated with acetyl chloride to give the acyl glycine 16. The acylated glycine is coupled with an appropriately protected tryptophan (wherein R is H or methyl) to give 17. The heterocyclic ring is prepared using the appropriate reagents (for example, DBU, carbon tetrachloride and triphenylphosphine to prepare an oxazole, ammonium acetate to prepare an imidazole and Lawesson's reagent to prepare a thiazole) to give compound 18. This intermediate is either elaborated in a stepwise manner (Method A) or in a convergent manner (Method B) to give the final product. In Method A, the Boc group is removed and the residue is coupled with Boc-Leucyl-OH to give compound 19. The Boc nitrogen protecting group is removed and the residue is coupled with N-methyl-N-phenylcarbamoyl chloride. Hydrogenolysis of the benzyl ester provides the final product 20. Alternatively in Method B, the heterocyclic intermediate is de-protected, coupled with N-(N-methyl-N-phenylaminocarbonyl)-Leucyl-OH and the benzyl group hydrogenolyzed to give the final product 20.

The preparation of a compound wherein Q is a cyclic urea or a cyclic thiourea is shown in Scheme V. An amino acid 21 (wherein P_3 is loweralkyl) is protected with a carbamate N-protecting group (for example, Cbz) to give tertiary amine 22 (wherein P_2 is a carbamate N-protecting group). The carboxy protecting group is hydrolyzed (for example, using lithium hydroxide in water/THF) and then the compound is coupled with amino acid 23 (wherein P_4 is loweralkyl, preferably tertiary-butyl). The resulting carboxamide is reduced to the amine using borane to give diamine 24. The N-protecting group is removed (for example, by catalytic hydrogenation using palladium on carbon catalyst) and the resulting diamine is cyclized (for example, using carbonyldimidazole to give the imidazolidone (A is -C(O)-) or using sulfuryl chloride in pyridine to give the imidazolidinethione (A is $-S(O)_2-$)). The carboxy protecting group is removed (for example, using

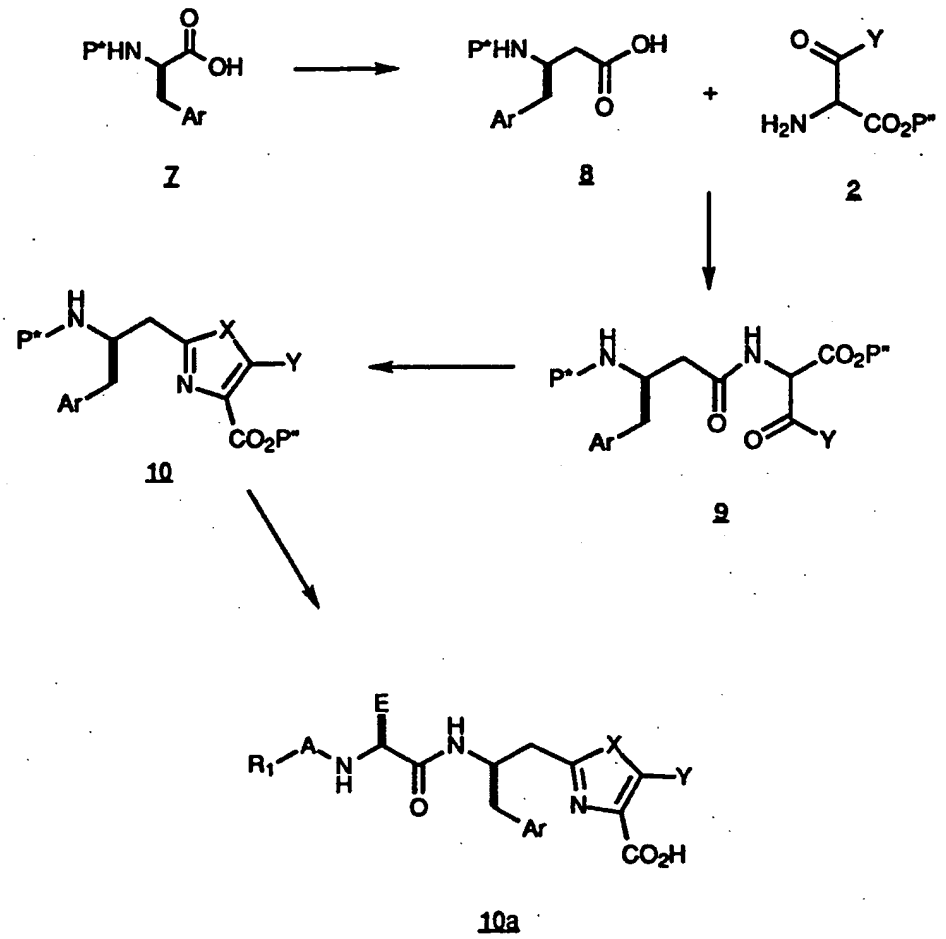
hydrochloric acid in dioxane) and the resulting carboxylic acid is coupled with an amino acid 14* (compound 14 from Scheme III in which the amino protecting group has been removed) resulting in compound 26.

5

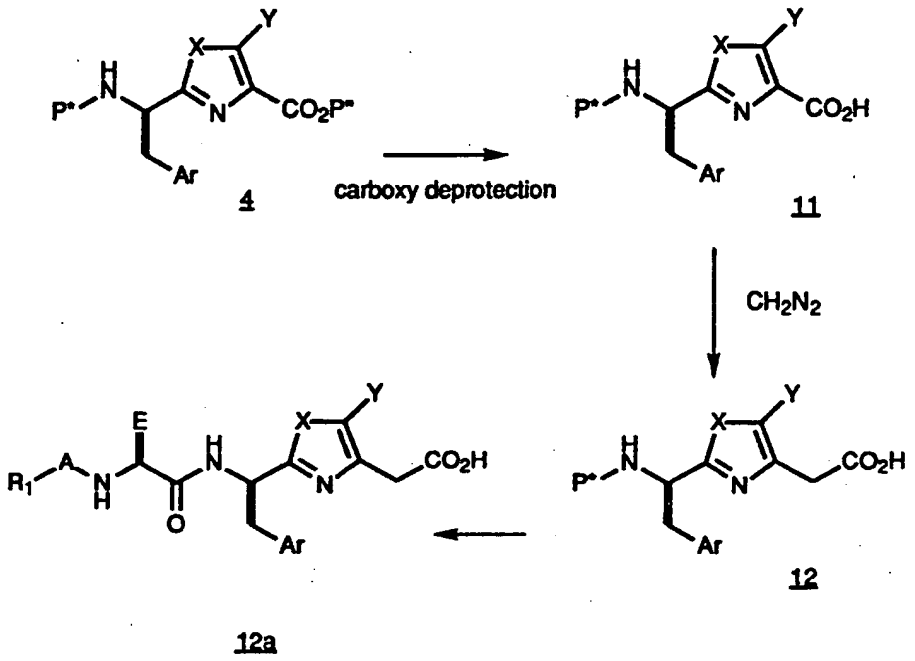
Scheme I


1. LiHMDS
2. YCOCl
3. H+
1
2
3
4
5
6
Method A:
1. deprotect
2. couple with
P-NH-CH(E)CO2H
Method B;
1. deprotect terminal amino
2. couple with
R1-A-NHCH(E)CO2H
3. deprotect carboxy
Method A (cont.):
1. deprotect terminal amino
2. acylate with R1-A-Cl
3.deprotect carboxy
-or-
Method C:
1. deprotect carboxy
(for R1-A = P)

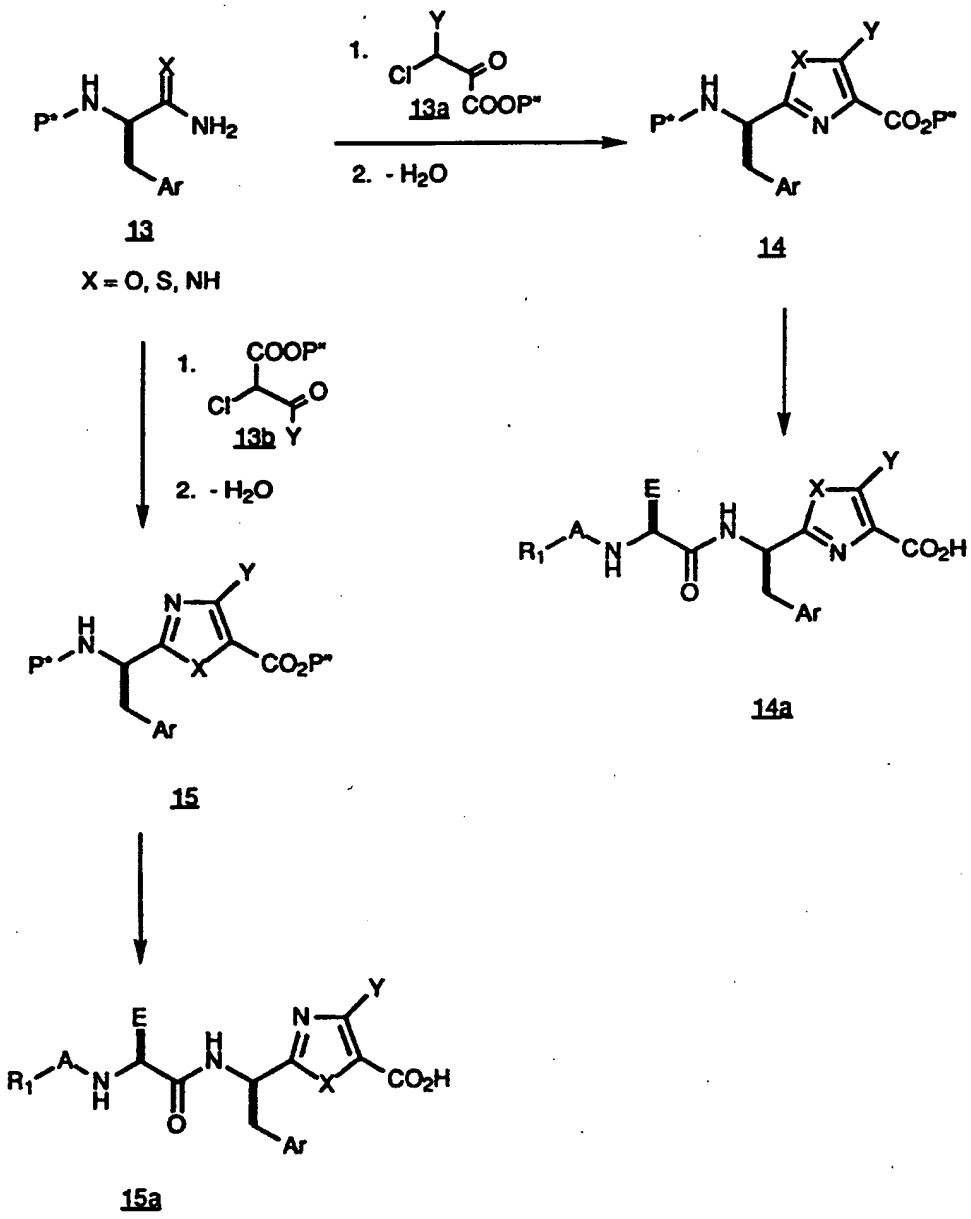
Scheme II



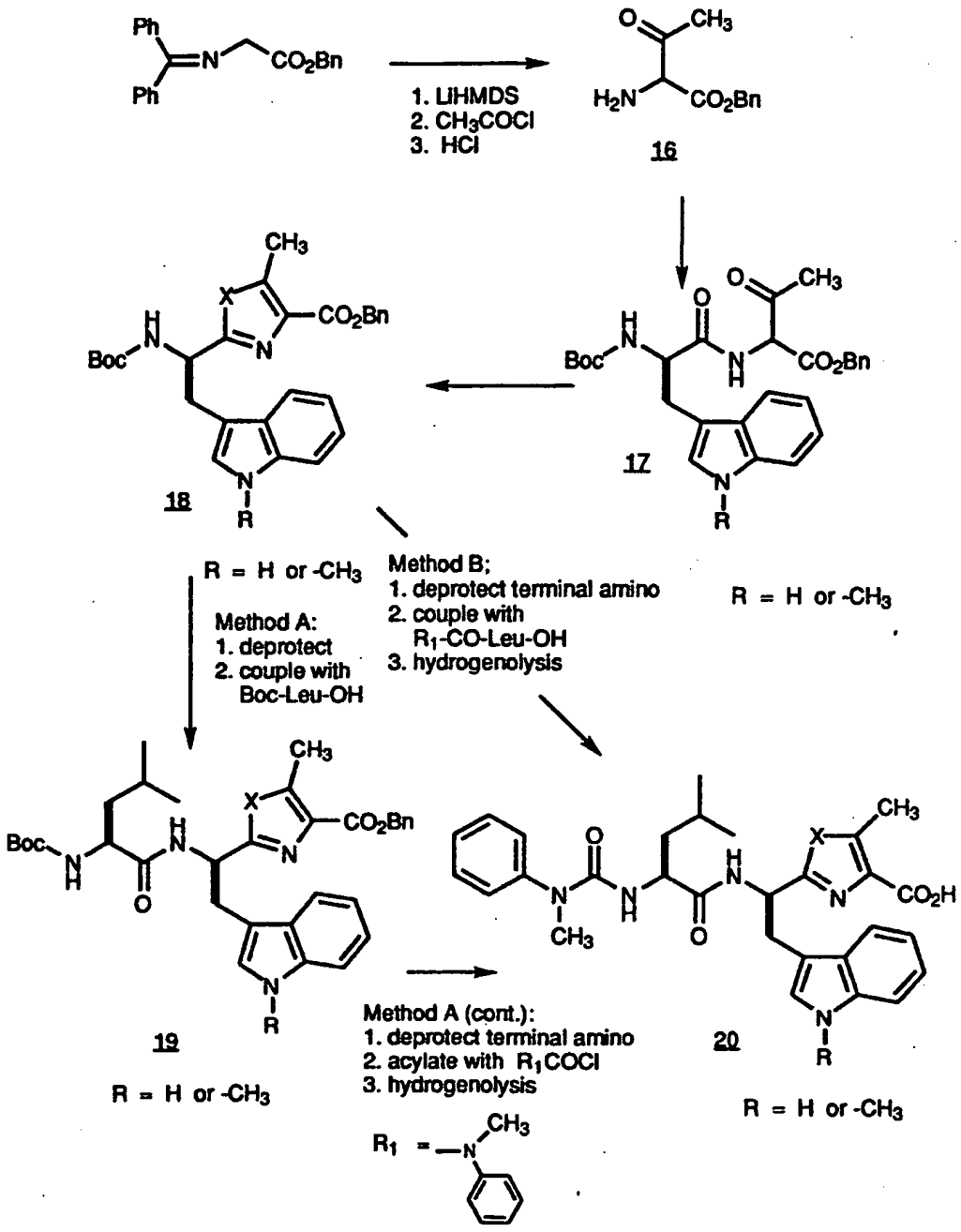
Scheme II cont.



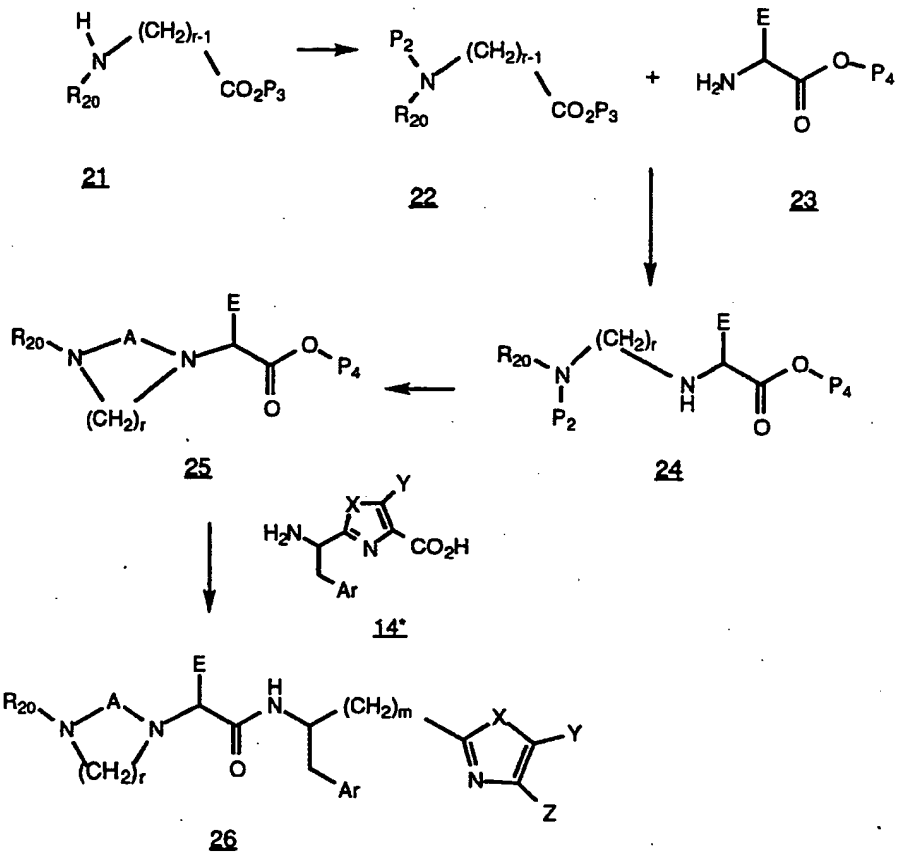
Scheme III



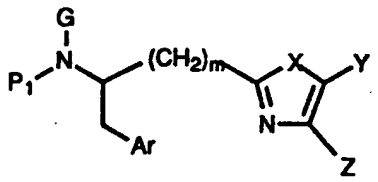
Scheme IV


Ph
Ph
N
CO2Bn
1. LiHMDS
2. CH3COCl
3. HCl
O
CH3
H2N
CO2Bn
16
Boc
N
H
X
N
CO2Bn
CH3
N
R
18
R = H or -CH3
Method A:
1. deprotect
2. couple with
Boc-Leu-OH
Method B;
1. deprotect terminal amino
2. couple with
R1-CO-Leu-OH
3. hydrogenolysis
17
R = H or -CH3
19
R = H or -CH3
Method A (cont.):
1. deprotect terminal amino
2. acylate with R1COCl
3. hydrogenolysis
R1 =
CH3
20
CO2H
R = H or -CH3

Scheme V



Compounds which are useful as intermediates for the preparation of the compounds of the invention are:



(III)

wherein

P_1 is hydrogen or an N-protecting group;

m is 0, 1 or 2;

X is $-N(R_2)-$, -O- or -S-, wherein R_2 is hydrogen, loweralkyl, arylalkyl or (heterocyclic)alkyl;

G is hydrogen or loweralkyl;

Ar is bicyclic aryl or bicyclic heteroaryl; and

Y and Z are independently selected from the group consisting of

(1) hydrogen;

(2) loweralkyl;

(3) loweralkyl substituted with one, two or three groups independently selected from cyano, hydroxy, alkoxy, amino, alkylamino, dialkylamino, azido, thioalkoxy, and halo;

(4) cycloalkyl;

(5) (cycloalkyl)alkyl;

(6) aryl;

(7) arylalkyl;

(8) a radical of the formula $-(CH_2)_n-C(O)-W$ wherein W is $-OR_{10}$ wherein R_{10} is hydrogen or a carboxy protecting group, amino, alkylamino, dialkylamino, hydroxyamino, N-hydroxyl-N-alkylamino or a naturally occurring α-amino acid wherein the

amino acid is bonded through the α-amino group;

(9) a radical of the formula $-(CH_2)_n-V$ wherein V is

(a) $-S(O)_2NHC(O)R_{16}$ wherein R_{16} is loweralkyl, haloalkyl, or phenyl,

(b) $-PO_3H_2$,

(c) -P(O)(OH)E wherein E is hydrogen, loweralkyl or arylalkyl,

(d) -CN,

(e) $-C(O)NHR_{17}$ wherein R_{17} is loweralkyl,

(f) alkylaminocarbonyl,

(g) dialkylaminocarbonyl,

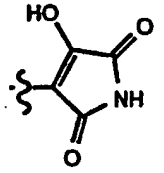
(h) tetrazolyl,

(i) hydroxy,

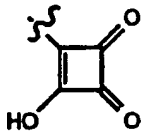
(j) alkoxy,

(k) sulfonamido,

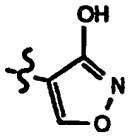
(l) $-C(O)NHS(O)_2R_{16}$ wherein R_{16} is defined as above,

(m) 

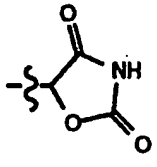
,

(n) 

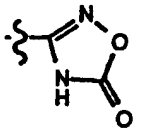
,

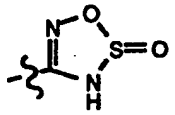
(o) 

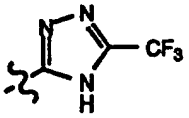
,

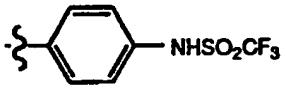
(p) 

.

(q)  ,

(r)  ,

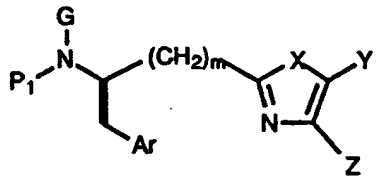
(s)  , or

(t)  ; and

(10) $-(CH_2)_n-NHS(O)_2R_6$ wherein R_6 is loweralkyl or haloalkyl and wherein at each occurrence n as used above is independently selected from 0, 1 or 2;

with the proviso that at least one of Y or Z is a radical of the formula $-(CH_2)_n-C(O)-W$, $-(CH_2)_n-V$ or $-(CH_2)_n-NHS(O)_2R_6$ wherein n, W, V and R_6 are defined as above; and

a compound of the formula



(IV)

wherein

P_1 is hydrogen or an N-protecting group;

m is 0, 1 or 2;

X is $-N(R_2)-$, -O- or -S-, wherein R_2 is hydrogen, loweralkyl, arylalkyl or (heterocyclic)alkyl;

G is hydrogen or loweralkyl;

Ar is bicyclic aryl or bicyclic heteroaryl; and

Y and Z are independently selected from the group consisting of

(1) hydrogen;

(2) loweralkyl;

(3) loweralkyl substituted with one, two or three groups independently selected from cyano, hydroxy, alkoxy, amino, alkylamino, dialkylamino, azido, thioalkoxy, and halo;

(4) cycloalkyl;

(5) (cycloalkyl)alkyl;

(6) aryl;

(7) arylalkyl;

(8) a radical of the formula $-(CH_2)_n-C(O)-W$ wherein W is $-OR_{10}$ wherein R_{10} is hydrogen or a carboxy protecting group, amino, alkylamino, dialkylamino, hydroxyamino, N-hydroxyl-N-alkylamino or a naturally occurring α-amino acid wherein the amino acid is bonded through the α-amino group;

(9) a radical of the formula $-(CH_2)_n-V$ wherein V is

(a) $-S(O)_2NHC(O)R_{16}$ wherein R_{16} is loweralkyl, haloalkyl, or phenyl,

(b) $-PO_3H_2$,

(c) -P(O)(OH)E wherein E is hydrogen, loweralkyl or arylalkyl,

(d) -CN,

(e) $-C(O)NHR_{17}$ wherein R_{17} is loweralkyl,

(f) alkylaminocarbonyl,

(g) dialkylaminocarbonyl,

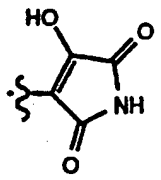
(h) tetrazolyl,

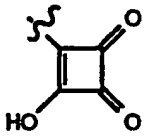
(i) hydroxy,

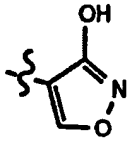
(j) alkoxy,

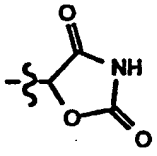
(k) sulfonamido,

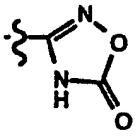
(l) $-C(O)NHS(O)_2R_{16}$ wherein R_{16} is defined as above,

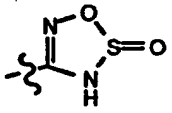
(m)  ,

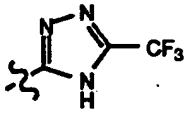
(n)  ,

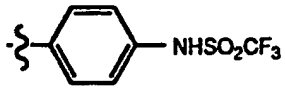
(o)  ,

(p)  ,

(q)  ,

(r)  ,

(s)  , or

(t)  ; and

(10) $-(CH_2)_n-NHS(O)_2R_6$ wherein R_6 is loweralkyl or haloalkyl and wherein at each occurrence n as used above is independently selected from 0, 1 or 2;

with the proviso that at least one of Y or Z is a radical of the formula $-(CH_2)_n-C(O)-W$, $-(CH_2)_n-V$ or $-(CH_2)_n-NHS(O)_2R_6$ wherein n, W, V and R_6 are defined as above.

Preferred intermediates include compounds of formula (III) or (IV) wherein

Y is

(1) hydrogen;
(2) loweralkyl;
(3) loweralkyl substituted with one, two or three substituents independently selected from the group consisting of cyano, hydroxy, alkoxy, amino, alkylamino, dialkylamino, thioalkoxy, and halo;
(4) cycloalkyl;
(5) (cycloalkyl)alkyl;
(6) aryl;
(7) arylalkyl or
(8) a radical of the formula $-(CH_2)_n-C(O)-W$ wherein W is $-OR_{10}$ wherein R_{10} is hydrogen or a carboxy protecting group, and

Z is

(1) a radical of the formula $-(CH_2)_n-C(O)-W$ wherein W is $-OR_{10}$, wherein R_{10} is hydrogen or a carboxy protecting group, amino, alkylamino, dialkylamino, hydroxyamino, N-hydroxyl-N-alkylamino and a naturally occurring α-amino acid wherein the amino acid is bonded through the α-amino group;
(2) $-(CH_2)_n-$(tetrazolyl) or
(3) $-(CH_2)_n-NHS(O)_2R_6$ wherein R_6 is loweralkyl or haloalkyl and at each occurrence n as used above is independently selected from 0, 1 or 2; and

compounds of formula (III) or (IV) wherein

Y is

(1) a radical of the formula $-(CH_2)_n-C(O)-W$ wherein W is $-OR_{10}$, wherein R_{10} is hydrogen or a carboxy protecting group, amino, alkylamino, dialkylamino, hydroxyamino, N-hydroxyl-N-alkylamino and a naturally occurring α-amino acid wherein the amino acid is bonded through the α-amino group;

(2) $-(CH_2)_n$-(tetrazolyl) or

(3) $-(CH_2)_n-NHS(O)_2R_6$ wherein R_6 is loweralkyl or haloalkyl; and

Z is

(1) hydrogen;

(2) loweralkyl;

(3) loweralkyl substituted with one, two or three substituents independently selected from the group consisting of cyano, hydroxy, alkoxy, amino, alkylamino, dialkylamino, thioalkoxy, and halo;

(4) cycloalkyl;

(5) (cycloalkyl)alkyl;

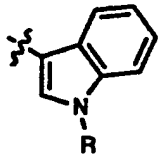
(6) aryl;

(7) arylalkyl or

(8) a radical of the formula $-(CH_2)_n-C(O)-W$ wherein W is $-OR_{10}$ wherein R_{10} is hydrogen or a carboxy protecting group and at each occurrence n as used above is independently selected from 0, 1 or 2.

Particularly preferred intermediates are compounds of formula (III) or (IV) wherein

G is hydrogen;

Ar is  wherein R is hydrogen or loweralkyl;

Y is loweralkyl;

Z is a radical of the formula -CO-W, wherein W is $-OR_{10}$, wherein R_{10} is hydrogen or a carboxy protecting group;

m is 0 or 1; and

X is -NH- or -O- .

The foregoing may be better understood by reference to the following examples which are provided for illustration and not intended to limit the scope of the inventive concept. The following abbreviations are used: Boc for tert-butyloxycarbonyl, Cbz for benzyloxycarbonyl, Cha for cyclohexylalanine, DBU for 1,8-diazabicyclo[5.4.0]undec-7-ene, DMAP for dimethylaminopyridine, EDCI for 1-(3-dimethylaminopropyl-3-ethylcarbodiimide hydrochloride, Et_3N for triethylamine, EtOAc for ethyl acetate, EtOH for ethanol, HOAc for acetic acid, HOBt for 1-hydroxybenzotriazole, LiHMDS for lithium hexamethyldisilazide, MeOH for methanol, *p*-TsOH for *para*-toluenesulfonic acid, Et_3N for triethylamine, TFA for trifluoroacetic acid, Pd/C for palladium on carbon and THF for tetrahydrofuran.

Example 1

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid

Example 1A

Cbz-D-Tryptophanyl-(2-acetylGlycine) ethyl ester

N-(Diphenylmethylene)glycine ethyl ester (30.0 g) was dissolved in THF (125 mL) and the solution cooled to -78 °C. Lithium hexamethyldisilazide (100 mL, 1 N solution in THF) was added slowly over 10 minutes, and the resulting yellow slurry was stirred at -78 °C for 45 minutes. The slurry was then transferred via cannula to a solution of acetyl chloride (8.4 mL) in THF (50 mL) at -78 °C . Additional THF (250 mL) was added to the anion solution to facilitate transfer to the acetyl chloride solution. Complete transfer of the anion took about 2.5 hours. After the addition was complete, the reaction was allowed to warm to room temperature and stirring was continued for four hours. The reaction was then quenched with 2 N HCl (115 mL). The THF was evaporated and the resulting aqueous solution was washed with EtOAc (2 x 100 mL). The organic phases were discarded and the aqueous phase was concentrated *in vacuo*. The resulting slurry was treated with EtOH (150 mL) and the insolubles filtered off. The filtrate was evaporated to give 2-acetylglycine ethyl ester hydrochloride as a yellow solid which was used without further purification.

Cbz-D-Tryptophan (40.6 g) was dissolved in THF (100 mL) and the solution cooled to -20 °C. N-Methylmorpholine (13 mL) was added followed by the dropwise addition of isobutylchloroformate (15.6 mL). After the addition was complete, the reaction was stirred for 30 minutes at -20 °C at which time the bath was removed. The 2-acetylglycine ester from above was dissolved in DMF (50 mL) and added to the mixed anhydride. N-Methylmorpholine (13 mL) was then added via syringe pump over a one hour period. After the addition was complete, the reaction was allowed to stir at room temperature for one hour. Water (200 mL) was added and the layers separated. The organic layer was

washed with saturated $NaHCO_3$ solution, 1 N H_3PO_4 and brine, dried with $MgSO_4$, and evaporated under reduced pressure to give an orange oil which was purified by flash chromatography on silica gel eluting with 15% EtOAc-hexane. The title compound was isolated as an orange oil (30.7 g, 59% yield for the two steps). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.26 (dt, 3H, J=1Hz,7Hz), 2.24 (s, 1.5H), 2.30 (s, 1.5H), 3.20 (m, 1H), 3.35 (m, 1H), 4.22 (dq, 2H, J=1Hz,7Hz), 4.50 (m, 1H), 5.06 (dd, 1H, J=7Hz,8Hz), 5.12 (s, 2H), 5.45 (m, 1H), 6.82 (m, 1H), 7.23 (m, 9H), 7.65 (m, 1H), 8.10 (s, 1H). MS (DCI/NH_3) m/e 466 $(M+H)^+$, 483 $(M+NH_4)^+$.

Example 1B

2-{(1R)-1-(Benzyloxycarbonylamino)-2-(indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid ethyl ester

The compound resulting from Example 1A (5.0 g) was dissolved in acetic acid (15 mL). Ammonium acetate (4.0 g) was added and the mixture heated at reflux for 16 hours. After cooling, the solvent was evaporated under reduced pressure and the residue taken up in saturated $NaHCO_3$ solution and extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$ and evaporated *in vacuo*. The resulting orange oil was purified by flash chromatography on silica gel eluting with 25% EtOAc-hexane to afford 3.60 g (73%) of the title compound. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.31 (t, 3H, J=7Hz), 2.43 (s, 3H), 3.37 (m, 1H), 3.47 (m, 1H), 4.27 (q, 2H, J=7Hz), 5.03 (s, 2H), 5.07 (m, 1H), 5.26 (br s, 1H), 6.82 (s, 1H), 7.04(t, 1H, J=8Hz), 7.16 (t, 1H, J=8Hz), 7.30 (m, 5H), 7.50 (d, 1H, J=8Hz), 8.05 (s, 1H). MS (DCI/NH_3) m/e 447 $(M+H)^+$.

Example 1C

2-[(1R)-1-Amino-2-(indol-3-yl)ethyl]-5-methyl-imidazole-4-carboxylic acid ethyl ester

The compound resulting from Example 1B (1.7 g) was dissolved in EtOH (10 mL). The solution was purged of oxygen, 10% Pd/C (0.5 g) was added, and the mixture was stirred at room temperature under an atmosphere of hydrogen. After two hours the catalyst was removed by filtration and the solvent evaporated *in vacuo* to give a white solid (1.2 g).

Example 1D

N-(Homopiperidin-1-ylcarbonyl)-Leucyl-OH

Leucyl-OBn · pTsOH (100 mg) was dissolved in $CHCl_3$ (2 mL). Et_3N (51 mg, 75 µL) was added and the solution cooled to 0 °C in an ice bath. Carbonyldiimidazole (41 mg) was added and the solution stirred at 0 °C for one hour. The bath was removed and the solution was stirred an additional one hour at room temperature. Homopiperidine (44 mg, 50 µL) was added and the solution stirred overnight at room temperature. The solution was washed with saturated $NaHCO_3$ solution, 1 N H_3PO_4 and brine, dried with $MgSO_4$, and evaporated under reduced pressure to give a white solid which was purified by flash chromatography on silica gel eluting with 25% EtOAc-hexane to give N-(homopiperidin-1-ylcarbonyl)-leucine benzyl ester (77 mg, 88%). The ester was dissolved in EtOH (5 mL), the solution purged of oxygen, 10% Pd/C (0.10g) added and the mixture stirred under hydrogen for two hours. The solvent was removed *in vacuo* and the residue taken up in EtOAc and filtered through Celite® to remove the catalyst. The solvent was evaporated *in vacuo* to give the carboxylic acid as a white solid (55 mg, 96%).

Example 1E

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid ethyl ester

The compound resulting from Example 1C (68 mg) was dissolved in THF (2 mL). HOBt (30 mg), the acid prepared in Example 1D (55 mg) and EDCI (42 mg) were added. N-Methylmorpholine (10 µL) and DMF (1 mL) were added and the mixture stirred at room temperature for 18 hours. The solvent was evaporated under reduced pressure and the residue taken up in EtOAc. The solution was washed with saturated $NaHCO_3$ solution, 1 N H_3PO_4 and brine, dried with $MgSO_4$, and evaporated *in vacuo* to give an orange oil which was purified by flash chromatography on silica gel eluting with 50% EtOAc-hexane.

Example 1F

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid

The compound resulting from Example 1E was dissolved in THF (2 mL) and a solution of LiOH (50 mg) in H_2O (1 mL) was added. The mixture was heated in a Carius tube at 110 °C for 15 hours. The solvents were evaporated under reduced pressure and the residue taken up in 1 N H_3PO_4 (5 mL). The suspension was dissolved in water and acetonitrile, and the product purified by preparative HPLC (Vydac µC18) eluting with a 10-70% gradient of CH_3CN in 0.1% TFA. The desired fractions were lyophilized to give the product (and its diastereomer) as a white solid. ^1H NMR (CD_3OD, 300 MHz) δ 0.77 (d, 3H, J=7Hz), 0.82 (d, 3H, J=7Hz), 1.30 (m, 2H), 1.52 (m, 5H), 1.66 (m, 4H), 2.52 (s, 3H), 3.4 (m, 6H), 3.59 (dd, 1H, J=7Hz,15Hz), 4.07 (dd, 1H, J=5Hz,9Hz), 5.42 (dd, 1H, J=6Hz,8Hz), 7.01 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.11 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.12 (s, 1H), 7.36 (d, 1H, J=8Hz), 7.45 (d, 1H, J=8Hz). MS (DCI/NH_3) m/e 523 $(M+H)^+$. Anal calcd for $C_{28}H_{38}N_6O_4 \cdot 1.5$ TFA: C, 53.68; H, 5.74; N, 12.12. Found: C, 53.60; H, 5.85; N, 12.08.

Example 2

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid

The title compound was prepared according to the procedures described in Example 1 but substituting Cbz-D-(1-methyl)Trp-OH for Cbz-D-Trp-OH in Example 1A. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.93 (d, 3H, J=7Hz), 0.96 (d, 3H, J=7Hz), 1.30 (m, 2H), 1.52 (m, 5H), 1.66 (m, 4H), 2.52 (s, 3H), 3.4 (m, 5H), 3.59 (dd, 1H, J=7Hz,15Hz), 3.75 (s, 3H), 4.07 (dd, 1H, J=7Hz,8Hz), 4.35 (dd, 1H, J=6Hz,10Hz), 5.42 (dd, 1H, J=6Hz,8Hz), 7.04 (s, 1H), 7.05 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.18 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.35 (d, 1H, J=8Hz), 7.47 (d, 1H, J=8Hz). MS (DCI/NH_3) m/e 537 $(M+H)^+$. HRMS Calcd for $C_{29}H_{41}N_6O_4$: 537.3189. Found: 537.3191.

Example 3

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-phenyl-imidazole-4-carboxylic acid

The title compound was prepared according to the procedures described in Example 1 but substituting benzoyl chloride for acetyl chloride in Example 1A. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.80 (d, 3H, J=6Hz), 0.85 (d, 3H, J=6Hz), 1.2-1.45 (m, 10H), 3.2 (m, 4H), 3.43 (dd, 1H, J=8Hz,15Hz), 3.52 (dd, 1H, J=6Hz,7Hz), 3.62 (dd, 1H, J=6Hz,15Hz), 4.13 (t, 1H, J=7Hz), 5.43 (dd, 1H, J=6Hz,8Hz), 6.96 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.10 (ddd, 1H, J=2Hz,7Hz,8Hz), 7.14 (s, 1H), 7.36 (ddd, 1H, J=1Hz,2Hz,8Hz), 7.45 (m, 4H), 7.69 (dt, 1H, J=2Hz,8Hz), 7.57 (dd, 1H, J=2Hz,7Hz). MS (FAB+NBA) m/e 585 $(M+H)^+$, 647 $(M+Cu)^+$. Anal calcd for $C_{33}H_{40}N_6O_4 \cdot 1.25$ TFA: C, 58.63; H, 5.72; N, 11.56. Found: C, 58.64; H, 5.91; N, 11.71.

Example 4

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-benzyl-imidazole-4-carboxylic acid

The title compound was prepared according to the procedures described in Example 1 but substituting phenylacetyl chloride for acetyl chloride in Example 1A. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.81 (d, 3H, J=6Hz), 0.85 (d, 3H, J=6Hz), 1.36 (m, 1H), 1.51 (m, 5H), 1.63 (m, 5H), 3.2-3.6 (m, 7H), 4.09 (dd, 1H, J=6Hz,8Hz), 4.24 (d, 1H, J=15Hz), 4.36 (d, 1H, J=15Hz), 5.37 (dd, 1H, J=7Hz,8Hz), 6.94 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.04 (s, 1H), 7.1 (d, 2H, J=8Hz), 7.2-7.3 (m, 4H), 7.34 (dd, 2H, J=1Hz,8Hz). MS (FAB+G/SG) m/e 599 $(M+H)^+$. Anal calcd for $C_{34}H_{42}N_6O_4 \cdot 1.75$ TFA: C, 56.42; H, 5.52; N, 10.53. Found: C, 56.14; H, 5.68; N, 10.65.

Example 5

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-ethyl-imidazole-4-carboxylic acid

The title compound was prepared according to the procedures described in Example 1 but substituting propionyl chloride for acetyl chloride in Example 1A. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.81 (d, 3H, J=6Hz), 0.85 (d, 3H, J=7Hz), 1.15 (t, 3H, J=8Hz), 1.3-1.4 (m, 2H), 1.53 (m, 5H), 1.67 (m, 4H), 2.9 (m, 2H), 3.3-3.6 (m, 6H), 4.10 (dd, 1H, J=6Hz,8Hz), 5.36 (dd, 1H, J=7Hz,8Hz), 6.98 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.10 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.12 (s, 1H), 7.36 (d, 2H, J=8Hz). MS (DCI/NH_3) m/e 537 $(M+H)^+$. Anal calcd for $C_{29}H_{40}N_6O_4 \cdot 1.6$ TFA: C, 53.78; H, 5.83; N, 11.69. Found: C, 53.94; H, 5.94; N, 11.23.

Example 6

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-propyl-imidazole-4-carboxylic acid

The title compound was prepared according to the procedures described in Example 1 but substituting butyryl chloride for acetyl chloride in Example 1A. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.79 (d, 3H,

J=6Hz), 0.84 (d, 3H, J=7Hz), 0.88 (t, 3H, J=8Hz), 1.3-1.4 (m, 2H), 1.53 (m, 5H), 1.60 (m, 2H), 1.68 (m, 4H), 2.94 (m, 2H), 3.3-3.6 (m, 6H), 4.10 (dd, 1H, J=7Hz,9Hz), 5.35 (dd, 1H, J=7Hz,8Hz), 6.97 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.07 (s, 1H), 7.10 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.35 (d, 1H, J=8Hz), 7.40 (d, 1H, J=8Hz). MS (DCI/NH_3) m/e 551 $(M+H)^+$. Anal calcd for $C_{30}H_{42}N_6O_4 \cdot 1.2$ TFA: C, 56.60; H, 6.33; N, 12.22. Found: C, 56.30; H, 6.46; N, 12.13.

Example 7

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-isopropyl-imidazole-4-carboxylic acid

The title compound was prepared according to the procedures described in Example 1 but substituting isovaleryl chloride for acetyl chloride in Example 1A. ^1H NMR (CD_3OD, 300 MHz) δ 0.85 (d, 3H, J=6Hz), 0.87 (d, 3H, J=6Hz), 1.10 (d, 3H, J=7Hz), 1.21 (d, 3H, J=7Hz), 1.4-1.5 (m, 2H), 1.52 (m, 5H), 1.68 (m, 4H), 3.3-3.5 (m, 6H), 3.72 (m, 1H), 4.10 (dd, 1H, J=6Hz,10Hz), 5.29 (t, 1H, J=6Hz), 6.96 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.09 (s, 1H), 7.12 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.24 (d, 1H, J=8H z), 7.35 (td, 1H, J=1Hz,8Hz). MS (FAB+NBA) m/e 551 $(M+H)^+$, 573 $(M+Na)^+$. Anal calcd for $C_{30}H_{42}N_6O_4 \cdot 1.6$ TFA: C, 54.39; H, 5.99; N, 11.46. Found: C, 54.46; H, 6.38; N, 11.31.

Example 8

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-cyclopropyl-imidazole-4-carboxylic acid

The title compound was prepared according to the procedures described in Example 1 but substituting cyclopropanecarbonyl chloride for acetyl chloride in Example 1A. ^1H NMR (CD_3OD, 300 MHz) δ 0.85 (d, 3H, J=6Hz), 0.88 (d, 3H, J=6Hz), 1.08 (d, 3H, J=7Hz), 1.13 (d, 3H, J=6Hz), 1.5-1.8 (m, 11H), 3.3-3.5 (m, 6H), 3.72 (m, 1H), 4.09 (dd, 1H, J=6Hz,10Hz), 5.38 (t, 1H, J=7Hz), 6.96 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.07 (s, 1H), 7.09 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.22 (d, 1H, J=8Hz), 7.35 (dd,

1H, J=1Hz,8Hz). MS (FAB+NBA) m/e 549 $(M+H)^+$. HRMS Calcd for $C_{30}H_{41}N_6O_4$: 549.3189. Found: 549.3210 .

Example 9

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid ethyl ester

The title compound was prepared according to the procedures described in Example 1A through 1E. ^1H NMR (CD_3OD, 300 MHz) δ 0.77 (d, 3H, J=6Hz), 0.83 (d, 3H, J=6Hz), 1.3-1.4 (m, 2H), 1.39 (t, 3H, J=7Hz), 1.52 (m, 5H), 1.66 (m, 4H), 2.52 (s, 3H), 3.4 (m, 6H), 3.57 (dd, 1H, J=7Hz,15Hz), 4.08 (dd, 1H, J=7Hz,9Hz), 4.41 (q, 2H, J=7Hz), 5.39 (dd, 1H, J=6Hz,8Hz), 7.00 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.11 (s, 1H), 7.12 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.35 (td, 1H, J=1Hz,8Hz), 7.44 (td, 1H, J=1Hz,8Hz). MS (FAB/NBA) m/e 551 $(M+H)^+$, 573 $(M+Na)^+$. Anal calcd for $C_{30}H_{42}N_6O_4 \cdot 1.5$ TFA: C, 54.92; H, 6.08; N, 11.64. Found: C, 55.03; H, 6.19; N, 11.75.

Example 10

2-{(1R)-1-[N-(N-Homopiperidin-1-ylcarbonyl-N-methyl-Leucyl)-amino]-2-(indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid

The title compound was prepared according to the procedures described in Example 1 but substituting N-methyl leucine benzyl ester for leucine benzyl ester in Example 1D. ^1H NMR of the major diastereomer (CD_3OD, 300 MHz) δ 0.80 (d, 3H, J=6Hz), 0.88 (d, 3H, J=6Hz), 1.3-1.8 (m, 11H), 2.49 (s, 3H), 2.74 (s, 3H), 3.2-3.6 (m, 6H), 4.00 (m, 1H), 5.35 (m, 1H), 7.00 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.10 (s, 1H), 7.11 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.34 (td, 1H, J=1Hz,8Hz), 7.46 (td, 1H, J=1Hz,8Hz). MS (FAB+NBA) m/e 537 $(M+H)^+$, 559 $(M+Na)^+$. HRMS Calcd. for $C_{29}H_{41}N_6O_4$: 537.3189 . Found: 537.3173.

Example 11

1,5-Dimethyl-2-{(1R)-1-[N-(homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-imidazole-4-carboxylic acid

The title compound was prepared by the procedures described in Example 1 but substituting methylamine hydrochloride for ammonium acetate in Example 1B. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.89 (d, 3H, J=7Hz),0.91 (d, 3H, J=7Hz), 0.78-1.74 (m, 11H), 2.35 (s, 3H), 3.20 (s, 3H), 3.38 (m, 4H), 3.50 (m, 2H), 4.27 (dd, 1H, J=5Hz,7Hz), 5.36 (dd, 1H, J=5Hz,7Hz), 6.96 (t, 1H, J=7Hz), 7.07 (s, 1H), 7.09 (t, 1H, J=7Hz), 7.27 (d, 1H, J=7Hz), 7.34 (d, 1H, J=7Hz). MS (FAB) m/z 537 $(M+H)^+$, 599 $(M+Na)^+$.

Example 12

1-Benzyl-2-{(1R)-1-[N-(homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid

The title compound was prepared by the procedures described in Example 1 but substituting benzylamine for ammonium acetate in Example 1B. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.86 (d, 3H, J=7Hz), 0.88 (d, 3H, J=7Hz), 1.32 (m, 1H), 1.50 (m, 6H), 1.67 (br m, 4H), 2.25 (s, 3H), 3.3-3.5 (m, 6H), 4.23 (dd, 1H, J=6Hz,8Hz), 5.06 (dd, 2H, J=8Hz,20Hz), 5.40 (t, 1H, J=8Hz), 6.88 (m, 3H), 7.02 (s, 1H), 7.10 (m, 2H), 7.25 (m, 3H), 7.34 (d, 1H, J=8Hz). MS (FAB) m/e 613 $(M+H)^+$, 635 $(M+Na)^+$. Anal calcd for $C_{35}H_{44}N_6O_4 \cdot 1.5$ TFA: C, 58.23; H, 5.85; N, 10.72. Found: C, 58.02; H, 6.01; N, 10.82.

Example 13

2-{(1R)-1-[N-(Cyclohexylaminocarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid

The title compound was prepared by the methods described in Example 1 but substituting cyclohexylamine for homopiperidine in Example 1D. ^{1}H NMR (CD_3OD, 300 MHz) for the major diastereomer δ 0.78 (d, 3H, J= 7Hz), 0.80 (d, 3H, J=7Hz), 1.2-1.85 (m, 14H), 2.53 (s, 3H), 3.35-3.6(m, 4H), 4.044 (m, 1H), 5.42 (t, 1H, J=8Hz), 7.00 (t, 1H,

J=7Hz), 7.10 (s, 1H), 7.12 (t, 1H, J=7Hz), 7.36 (d, 1H, J=8Hz), 7.45 (d, 1H, J=8Hz). Anal calcd for $C_{28}H_{38}N_6O_4 \cdot 1.5$ TFA: C, 53.68; H, 5.74; N, 12.12. Found: C, 53.67; H, 5.32; N, 12.07.

Example 14

2-{(1R)-1-[N-(4-Methoxymethoxypiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid

The title compound was prepared by the methods described in Example 1 but substituting 4-methoxymethoxypiperidine for homopiperidine in Example 1D. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.6-0.9 (m, 6H), 1.15-1.55 (m, 5H), 1.82 (m, 2H), 2.52 (s, 3H), 3.16 (m, 2H), 3.35 (s, 3H), 3.58 (m, 1H), 3.75 (m, 3H), 4.03 (t, 1H, J=7Hz), 4.68 (s, 2H), 5.42 (dd, 1H, J=5Hz,7Hz), 7.01 (t, 1H, J=7Hz), 7.10 (t, 1H, J=7Hz), 7.14 (s, 1H), 7.35 (d, 1H, J=7Hz), 7.48 (d, 1H, J=7Hz). MS (DCI/ NH_3) m/e 569 $(M+H)^+$. Anal calcd for $C_{29}H_{40}N_6O_6 \cdot 1.50$ TFA $\cdot 1.75$ H_20: C, 51.96; H, 5.65; N, 11.36. Found: C, 51.98; H, 5.90; N, 11.28.

Example 15

2-{(1R)-1-[N-(Homopiperidin-1-ylsulfonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid

Example 15A

N-(Homopiperidin-1-ylsulfonyl)-Leucine

Homopiperidine (6 mL) was dissolved in diethyl ether (250 mL) and cooled to 0 °C in an ice bath. HCl gas was bubbled through the solution and the resulting white solid collected by filtration and dried *in vacuo*. The solid was taken up in sulfuryl chloride (20 mL) and the mixture heated at reflux. The reaction became very thick and additional sulfuryl chloride (10 mL) was added and reflux continued for 16 hours. The remaining sulfuryl chloride was evaporated and the residue distilled (90-100 °C, 0.1 mm) to give homopiperidinesulfonyl chloride as a colorless oil (9.06 g, 86%).

To the sulfonyl choride (0.97 g) dissolved in DMF (10 mL) was added Leu-OBn · pTsOH (2.03g), Hünig's base (1.75 mL), and then DMAP (0.2 g), and the mixture was stirred at room temperature for 16 hours. The solution was diluted with ethyl acetate, washed with water, 2 N HCl, saturated $NaHCO_3$ solution, and brine, dried, and evaporated. Purification by flash chromatography (10% EtOAc-hexane) gave N-(homopiperidin-1-ylsulfonyl)-leucine benzyl ester as a white solid (0.88 g, 47%). The benzyl ester (0.85 g) was dissolved in MeOH (20 mL) and 10% Pd/C (0.75 g) was added. The mixture was stirred at room temperature under an H_2 atmosphere for 2.5 hours. The catalyst was filtered off and the solvent evaporated to give the product as a colorless oil (0.66 g, 100%).

Example 15B

2-[(1R)-1-[N-(Homopiperidin-1-ylsulfonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl]-5-methyl-imidazole-4-carboxylic acid

The title compound was prepared by the procedures described in Example 1 but substituting the compound resulting from Example 15A for N-(homopiperidin-1-ylcarbonyl)-Leucine in Example 1E. ^1H NMR (CD_3OD, 300 MHz) δ 0.83 (d, 3H, J=6Hz), 0.90 (d, 3H, J=6Hz), 1.4-1.8 (m, 11H), 2.49 (s, 3H), 2.57 (s, 3H), 2.88 (dd, 1H, J=9Hz,15Hz), 3.2-3.5 (m, 5H), 4.20 (dd, 1H, J=6Hz,11Hz), 5.34 (dd, 1H, J=7Hz,8Hz), 6.95 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.07 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.10 (s, 1H), 7.31 (td, 1H, J=1Hz,8Hz), 7.40 (td, 1H, J=1Hz,8Hz). MS (FAB+NBA) m/e 538 $(M+H)^+$,560 $(M+Na)^+$. Anal calcd for $C_{29}H_{39}N_5O_5 \cdot 1.0$ TFA: C, 57.14; H, 6.19; N, 10.75. Found: C, 56.76; H, 6.23; N, 10.71.

Example 16

2-[(1R)-1-[N-Boc-Leucyl-amino]-2-(indol-3-yl)ethyl]-5-methyl-imidazole-4-carboxylic acid

Example 16A

2-[(1R)-1-[(N-Boc-Leucyl)-amino]-2-(indol-3-yl)ethyl]-5-methyl-imidazole-4-carboxylic acid ethyl ester

2-[(1R)-1-Amino-2-(indol-3-yl)ethyl]-5-methyl-imidazole-4-carboxylic acid ethyl ester (1.2 g), prepared according to the method in Example 1C, was dissolved in THF (10 mL) and added to a solution of Boc-Leu-OH · H_2O (1.0 g) and HOBt (0.5 g) in THF (10 mL). EDCI (0.75 g) was added to the solution, followed by DMF (2 mL). The mixture was stirred for 20 hours at room temperature. The solvent was evaporated *in vacuo* and the residue taken up in EtOAc. The solution was washed with saturated $NaHCO_3$ solution, 1 N H_3PO_4, and brine, dried with $MgSO_4$, and evaporated to give an orange solid that was purified by flash chromatography (25% EtOAc-hexane) to give 1.85 g (92%) of the title compound. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.87 (d, 3H, J=7Hz), 0.89 (d, 3H, H=7Hz), 1.31 (t, 3H, J=7Hz), 1.45 (m, 3H), 1.52 (s, 9H), 2.46 (s, 3H), 3.27 (br s, 1H), 3.43 (m, 1H), 4.12 (m, 1H), 4.30 (q, 2H, J=7Hz), 5.50 (m, 1H), 6.65 (br s, 1H), 6.80-7.10 (m, 3H), 7.12 (s, 1H), 7.40 (m, 1H), 8.26 (m, 1H). MS (DCI/NH_3) m/e 526 $(M+H)^+$.

Example 16B

2-[(1R)-1-[(N-Boc-Leucyl)-amino]-2-(indol-3-yl)ethyl]-5-methyl-imidazole-4-carboxylic acid

The compound resulting from the procedure in Example 16A (100 mg) was dissolved in THF (2 mL) and a solution of LiOH (50 mg) in H_2O (1 mL) was added. The mixture was heated in a Carius tube at 110 °C for 15 hours. The solvents were evaporated under reduced pressure and the residue taken up in 1 N H_3PO_4 (5 mL). The suspension was dissolved in water and acetonitrile, and the product purified by preparative HPLC (Vydac μC18) eluting with a 10-70% gradient of

CH_3CN in 0.1% TFA. The desired fractions were lyophilized to give the product as a white solid. ^1H NMR (CD_3OD, 300 MHz) δ 0.87 (d, 3H, J=8Hz), 0.90 (d, 3H, J=8Hz), 1.28 (m, 2H), 1.41 (s, 9H), 1.59 (m, 1H), 2.47 (s, 3H), 3.50 (m, 2H), 4.05 (m, 1H), 5.35 (t, 1H, J=8Hz), 7.00 (m, 1H), 7.08 (m, 2H), 7.32 (m, 1H), 7.42 (d, 2H, J=8Hz). MS (FAB) m/e 498 $(M+H)^+$, 520 $(M+Na)^+$. Anal calcd for $C_{26}H_{35}N_5O_5 \cdot 1.25$ TFA: C, 53.48; H, 5.71; N, 10.94. Found: C, 53.49; H, 5.66; N, 11.24.

Example 17

2-[(1R)-1-[N-(Benzylaminocarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl]-5-methyl-imidazole-4-carboxylic acid

Example 17A

2-[(1R)-1-[N-(Benzylaminocarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl]-5-methyl-imidazole-4-carboxylic acid ethyl ester

The compound resulting from Example 16A (0.11 g) was taken up in 4 N HCl/dioxane (2 mL) and stirred at room temperature for 1 hour. The solvent was evaporated under reduced pressure and the residue taken up in EtOAc (10 mL). The solution was washed with saturated $NaHCO_3$ solution and brine, dried with $MgSO_4$ and evaporated *in vacuo* to give a white solid which was dissolved in THF (5 mL). Et_3N (50 µL) was added followed by benzyl isocyanate (38 mg, 35 µL). The solution was stirred at room temperature for 5 hours. The solvent was evaporated and the residue taken up in EtOAc. The solution was washed with saturated $NaHCO_3$ solution, 1 N H_3PO_4 and brine, dried with $MgSO_4$, and evaporated *in vacuo* to give the title compound as a white solid (100 mg).

Example 17B

2-{(1R)-1-[N-(Benzylaminocarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid

To the compound resulting from Example 17A (100 mg) dissolved in THF (3 mL) was added a solution of LiOH (0.1 g) in H_2O (3 mL). The mixture was heated in a Carius tube at 110 °C for 15 hours. The solvents were evaporated under reduced pressure and the residue taken up in 1 N H_3PO_4 (5 mL). The suspension was dissolved in water and acetonitrile and the product purified by preparative HPLC (Vydac μC18) eluting with a 10-70% gradient of CH_3CN in 0.1% TFA. The desired fractions were lyophilized to give the product as a white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.87 (d, 3H, J=7Hz), 0.89 (d, 3H, J=7Hz), 1.31 (t, 3H, J=7Hz), 1.45 (m, 3H), 1.52 (s, 9H), 2.46 (s, 3H), 3.27 (br s, 1H), 3.43 (m, 1H), 4.12 (m, 1H), 4.30 (q, 2H, J=7Hz), 5.50 (m, 1H), 6.65 (br s, 1H), 6.80-7.10 (m, 3H), 7.12 (s, 1H), 7.40 (m, 1H), 8.26 (m, 1H). MS (DCI/NH_3) m/e 526 $(M+H)^+$.

Example 18

2-{(1R)-1-[N-(Phenylacetyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid

The title compound was prepared according to the procedures described in Example 17 but substituting phenylacetyl chloride for benzyl isocyanate in Example 17A. ^1H NMR (CD_3OD, 300 MHz) of the major diastereomer δ 0.74 (d, 3H, J=8Hz), 0.79 (d, 3H, J=8Hz), 1.2-1.6 (m, 3H), 2.32 (s, 3H), 3.35 (m, 2H), 3.42-3.55 (m, 1H), 3.51 (d, 2H), 4.21 (m, 1H), 5.35 (m, 1H), 7.00 (m, 1H), 7.10 (t, 1H, J=7Hz), 7.2-7.3 (m, 6H), 7.33 (d, 1H, J=7Hz), 7.45 (d, 1H, J=7Hz). MS (DCI/NH_3) m/e 516 $(M+H)^+$. Anal calcd for $C_{29}H_{33}N_5O_4 \cdot 1.2$ TFA: C, 57.81; H, 5.28; N, 10.73. Found: C, 58.16; H, 5.08; N, 10.33.

Example 19

2-{(1R)-1-[N-(1-Naphthylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid

The title compound is prepared according to the procedures described in Example 17 but substituting 1-naphthoyl chloride for benzyl isocyanate in Example 17A.

Example 20

2-{(1R)-1-[N-(Cyclohexylacetyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid

Example 20A

2-{(1R)-1-[N-(Cyclohexylacetyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid ethyl ester

The compound resulting from Example 16A (0.10 g) was taken up in 4 N HCl in dioxane (2 mL) and stirred at room temperature for 1 hour. The solvent was evaporated under reduced pressure and the residue taken up in EtOAc (10 mL). The solution was washed with saturated $NaHCO_3$ solution and brine, dried with $MgSO_4$ and evaporated *in vacuo* to give a white solid which was dissolved in THF (5 mL). Cyclohexylacetic acid (0.027 g), HOBt (0.026 g), N-methylmorpholine (100 µL), and EDCI (0.37 g) were added. DMF (1 mL) was added and the mixture stirred at ambient temperature for 18 hours. The solvent was evaporated under reduced pressure and the residue taken up in EtOAc (10 mL). The solution was washed with saturated $NaHCO_3$ solution and brine, dried with $MgSO_4$ and evaporated *in vacuo* to give a white solid (105 mg).

Example 20B

2-{(1R)-1-[N-(Cyclohexylacetyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid

The compound resulting from Example 20A (100 mg) was dissolved in THF (3 mL) and a solution of LiOH (0.1 g) in H_2O (3 mL) was added. The mixture was heated in a Carius tube at 110 °C for 15 hours. The solvents were evaporated under reduced pressure and the residue taken up in 1 N H_3PO_4 (5 mL). The suspension was dissolved in water and acetonitrile, and the product purified by preparative HPLC (Vydac μC18) eluting with a 10-70% gradient of CH_3CN in 0.1% TFA. The desired fractions were lyophilized to give the product as a white solid. ^1H NMR (CD_3OD, 300 MHz) of the major diastereomer δ 0.76 (d, 3H, J=7Hz), 0.78 (d, 3H, J=7Hz), 0.89 (m, 3H), 1.1-1.5 (m, 7H), 1.58 (m, 6H), 2.00 (d, 2H, J=8Hz), 2.52 (s, 3H), 3.30 (m, 2H), 4.35 (m, 1H), 5.40 (m, 1H), 6.05 (m, 1H), 7.00 (s, 1H), 7.05 (m, 1H), 7.30 (d, 1H, J=7Hz), 7.44 (d, 1H, J=7Hz). MS (DCI/NH_3) m/e 522 $(M+H)^+$. Anal calcd for $C_{29}H_{39}N_5O_5 \cdot 1.25$ TFA: C, 56.97; H, 6.11; N, 10.54. Found: C, 57.10; H, 6.36; N, 10.70.

Example 21

2-{(1R)-1-[N-(Cycloheptylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid

The title compound was prepared according to the procedures described in Example 20 but substituting cycloheptanecarboxylic acid for cyclohexaneacetic acid in Example 20A. ^1H NMR (CD_3OD, 300 MHz) of the major diastereomer δ 0.76 (d, 3H, J=7Hz), 0.78 (d, 3H, J=7Hz), 1.2-1.8 (m, 15H), 2.42 (m, 1H), 2.51 (s, 3H), 3.53 (m, 2H), 4.18 (dd, 1H, J=6Hz,8Hz), 5.38 (m, 1H), 7.02 (m, 1H), 7.07 (m, 1H), 7.33 (m, 2H), 7.45 (d, 1H, J=7Hz). MS (DCI/NH_3) m/e 522 $(M+H)^+$. Anal calcd for $C_{29}H_{39}N_5O_5 \cdot 1.25$ TFA: C, 56.97; H, 6.11; N, 10.54. Found: C, 56.87; H, 6.31; N, 10.46.

Example 22

2-{(1R)-1-[N-(Norborn-2-ylacetyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid

The title compound was prepared according to the procedures described in Example 20 but substituting 2-norbornylacetic acid for cyclohexylacetic acid in Example 20A. ^{1}H NMR of the major diastereomer (CD_3OD, 300 MHz) δ 0.83 (d, 3H, J=6Hz), 0.91 (d, 3H, J=6Hz), 1.0-1.2 (m, 4H), 1.3-1.5 (m, 7H), 1.8-2.2 (m, 5H), 2.50 (s, 3H), 3.3-3.5 (m, 2H), 4.23 (m, 1H), 5.34 (ddd, 1H, J=3Hz,7Hz,8Hz), 7.01 (dt, 1H, J=1Hz,8Hz), 7.10 (dt, 1H, J=1Hz,8Hz), 7.11 (s, 1H), 7.35 (d, 1H, J=8Hz), 7.43 (d, 1H, J=8Hz). MS (DCI/NH_3) m/e 534 $(M+H)^+$. Anal calcd for $C_{30}H_{39}N_5O_4 \cdot 1.7$ TFA: C, 55.14; H, 5.64; N, 9.63. Found: C, 55.26; H, 5.73; N, 9.82.

Example 23

2-{(1R)-1-[N-(4-Methoxyphenylacetyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid

The title compound was prepared according to the procedures described in Example 20 but substituting 4-methoxyphenylacetic acid for cyclohexylacetic acid in Example 20A. ^{1}H NMR of the major diastereomer (DMSO-d_6, 300 MHz) δ 0.76 (d, 3H, J=6Hz), 0.82 (d, 3H, J=6Hz), 1.1-1.4 (m, 3H), 2.32 (s, 3H), 3.2-3.4 (m, 4H), 3.69 (s, 3H), 4.27 (m, 1H), 5.06 (m, 1H), 6.80 (td, 2H, J=2Hz,9Hz), 6.91 (s, 1H), 6.95 (dt, 1H, J=1Hz,8Hz), 7.04 (dt, 1H, J=1Hz,8Hz), 7.13 (td, 2H, J=2Hz,9Hz), 7.29 (d, 1H, J=8Hz), 7.57 (dd, 1H, J=1Hz,8Hz). MS (DCI/NH_3) m/e 546 $(M+H)^+$. Anal calcd for $C_{30}H_{35}N_5O_5 \cdot 1.4$ TFA: C, 55.86; H, 5.20; N, 9.93. Found: C, 55.50; H, 5.39; N, 10.04.

Example 24

2-[(1R)-1-[N-(3,3-Dimethylbutyryl)-Leucyl-amino]-2-(indol-3-yl)ethyl]-5-methyl-imidazole-4-carboxylic acid

The title compound was prepared according to the procedures described in Example 20 but substituting 3,3-dimethylbutyric acid for cyclohexylacetic acid in Example 20A. ^{1}H NMR of the major diastereomer (CD_3OD, 300 MHz) δ 0.78 (d, 3H, J=6Hz), 0.82 (d, 3H, J=6Hz), 0.95 (s, 9H), 1.1-1.4 (m, 3H), 2.08 (s, 2H), 2.49 (s, 3H), 3.4 (m, 4H), 4.20 (m, 1H), 5.20 (m, 1H), 6.98 (t, 1H, J=7Hz), 7.08 (s, 1H), 7.12 (t, 1H, J=7), 7.33 (d, 1H, J=8Hz), 7.45 (d, 1H, J=8Hz). MS (DCI/NH_3) m/e 496 $(M+H)^+$. Anal calcd for $C_{27}H_{37}N_5O_4 \cdot 1.35$ TFA: C, 54.92; H, 5.95; N, 10.78. Found: C, 54.72; H, 6.33; N, 10.95.'

Example 25

2-[(1R)-1-[N-(2-Propylvaleryl)-Leucyl-amino]-2-(indol-3-yl)ethyl]-5-methyl-imidazole-4-carboxylic acid

The title compound was prepared according to the procedures described in Example 20 but substituting 2-propylpentanoic acid for cyclohexylacetic acid in Example 20A. ^{1}H NMR of the major diastereomer (CD_3OD, 300 MHz) δ 0.85 (m, 12H), 1.1-1.6 (m, 11H), 2.28 (m, 1H), 2.49 (s, 3H), 3.55 (m, 2H), 4.26 (dd, 1H, J=6Hz,9Hz), 5.33 (dd, 1H, J=6Hz,7Hz), 7.00 (t, 1H, J=7Hz), 7.08 (s, 1H), 7.10 (t, 1H, J=7Hz), 7.29 (d, 1H, J=7Hz), 7.42 (d, 1H, J=7Hz). MS (DCI/NH_3) m/e 524 $(M+H)^+$. Anal calcd for $C_{29}H_{41}N_5O_4 \cdot 1.10$ TFA $\cdot$ 1.0 H_2O: C, 56.02; H, 6.68; N, 10.47. Found: C, 56.00; H, 6.71; N, 10.40.

Example 26

2-[(1R)-1-[N-(3-Pyridylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl]-5-methyl-imidazole-4-carboxylic acid

The title compound was prepared according to the procedures described in Example 20 but substituting nicotinic acid for cyclohexylacetic acid in Example 20A. ^{1}H NMR of the major diastereomer (CD_3OD, 300 MHz) δ 0.83 (d, 3H, J=6Hz), 0.85 (d, 3H, J=6Hz), 1.3-1.7 (m, 3H), 2.52 (s, 3H), 3.55 (m, 2H), 4.55 (dd, 1H, J=6Hz,7Hz), 5.42 (dd, 1H, J=6Hz,7Hz), 7.0 (t, 1H, J=7Hz), 7.08 (t, 1H, J=7Hz), 7.12 (s, 1H), 7.35 (d, 1H, J=8Hz), 7.62 (d, 1H, J=8Hz), 8.32 (t, 1H, J=7Hz), 8.72 (t, 1H, J=7Hz), 9.01 (d, 1H, J=7Hz). MS (DCI/NH_3) m/e 503 $(M+H)^+$. Anal calcd for $C_{27}H_{30}N_6O_4 \cdot 2.1$ TFA: C, 50.50; H, 4.36; N, 11.33. Found: C, 50.33; H, 4.59; N, 11.44.

Example 27

2-[(1R)-1-[N-(Cyclohexylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-imidazole-4-carboxylic acid

Example 27A

2-[(1R)-1-(Fmoc-amino)-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-imidazole-4-carboxylic acid benzyl ester

N-(Diphenylmethylene)glycine benzyl ester (4.1 g) was dissolved in THF (25 mL) and the solution cooled to -78 °C. Lithium hexamethyldisilazide (12.5 mL, 1 N solution in THF) was added slowly over 10 minutes, and the resulting yellow slurry was stirred at -78 °C for 30 minutes. The slurry was then transferred via cannula to a solution of acetyl chloride (0.93 mL) in THF (25 mL) at -78 °C . After the addition was complete, the reaction was allowed to warm to room temperature and stirring was continued for four hours. The reaction was then quenched with 2 N HCl (15 mL). The THF was evaporated and the resulting aqueous solution was washed with EtOAc (2 x 50 mL). The organic phases were discarded and the aqueous phase was concentrated *in vacuo*. The resulting slurry was treated with EtOH (100

mL) and the insolubles filtered off. The filtrate was evaporated to give 2-acetylglycine benzyl ester hydrochloride as a yellow solid which was used without further purification.

Fmoc-D-(1-methyl)-Tryptophan (5.75 g), prepared by the method of Cook, *et al.*, Chem. Pharm. Bull. 13 88 (1965), was dissolved in THF (20 mL) and the solution cooled to -20 °C. N-Methylmorpholine (1.45 mL) was added followed by the dropwise addition of isobutylchloroformate (1.7 mL). After the addition was complete, the reaction was stirred for 30 minutes at -20 °C at which time the bath was removed. The 2-acetylglycine ester from above was dissolved in DMF (20 mL) and added to the mixed anhydride. N-Methylmorpholine (1.45 mL) was then added via syringe pump over a one hour period. After the addition was complete, the reaction was allowed to stir at room temperature for one hour. Water (75 mL) was added and the layers separated. The organic layer was washed with saturated $NaHCO_3$ solution, 1 N H_3PO_4 and brine, dried with $MgSO_4$, and evaporated under reduced pressure to give an orange oil which was purified by flash chromatography on silica gel eluting with 15% EtOAc-hexane to give the product as a yellow solid (3.85 g, 49% yield for the two steps).

Example 27B

2-[(1R)-1-(Fmoc-amino)-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-imidazole-4-carboxylic acid benzyl ester

The compound resulting from Example 27A (5.0 g) was dissolved in acetic acid (25 mL). Ammonium acetate (4.0 g) was added and the mixture heated at reflux for 16 hours. After cooling, the solvent was evaporated under reduced pressure and the residue taken up in saturated $NaHCO_3$ solution and extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$ and evaporated *in vacuo*. The resulting orange oil was purified by flash chromatography on silica gel eluting with 25% EtOAc-hexane to afford 1.10 g (23%) of the title compound.

Example 27C

2-[(1R)-1-Amino-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-imidazole-4-carboxylic acid benzyl ester

The imidazole resulting from Example 27B (80 mg) was suspended in 3 mL of THF. Piperidine (0.3 mL) was added, and the resulting solution was stirred at ambient temperature for 45 minutes. The solvents were removed *in vacuo*, and the residue was triturated with hexanes, filtered, and dried under vacuum for 15 minutes to afford the title compound (50 mg, 100% yield).

Example 27D

N-(Cyclohexylaminocarbonyl)-Leucine

Leucine benzyl ester · *p*-TsOH (100 mg) was dissolved in $CHCl_3$ (2 mL). Et_3N (51 mg, 75 µL) was added and the solution cooled to 0 °C in an ice bath. Carbonyldiimidazole (41 mg) was added and the solution stirred at 0 °C for one hour. The bath was removed, and the solution was stirred an additional one hour at room temperature. Cyclohexylamine (44 mg, 50 µL) was added and the solution stirred overnight at room temperature. The solution was washed with saturated $NaHCO_3$ solution, 1 N H_3PO_4 and brine, dried with $MgSO_4$, and evaporated under reduced pressure to give a white solid which was purified by flash chromatography on silica gel eluting with 25% EtOAc-hexane to give N-(cyclohexylaminocarbonyl)-leucine benzyl ester (75 mg, 88%). The ester was dissolved in EtOH (5 mL), the solution was purged of oxygen, 10% Pd/C (0.10 g) was added, and the mixture was stirred under hydrogen for two hours. The solvent was removed *in vacuo* and the residue taken up in EtOAc and filtered through Celite® to remove the catalyst. The solvent was evaporated *in vacuo* to give the carboxylic acid as a white solid (50 mg, 90%).

Example 27E

2-{(1R)-1-[N-(Cyclohexylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-imidazole-4-carboxylic acid benzyl ester

The crude amine resulting from Example 27C (50 mg) was dissolved in THF (10 mL). HOBt (18 mg), N-(cyclohexylaminocarbonyl)-Leucine resulting from Example 27D (32 mg) and EDCI (25 mg) were added. N-Methylmorpholine (10 µL) and DMF (1 mL) were added and the mixture stirred at room temperature for 18 hours. The solvent was evaporated under reduced pressure and the residue taken up in EtOAc. The solution was washed with saturated $NaHCO_3$ solution, 1 N H_3PO_4 and brine, dried with $MgSO_4$, and evaporated *in vacuo* to give a yellow oil was purified by flash chromatography on silica gel eluting with 50% EtOAc-hexane to give the title compound (67 mg, 85 %).

Example 27F

2-{(1R)-1-[N-(Cyclohexylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-imidazole-4-carboxylic acid

To the benzyl ester resulting from Example 27E (65 mg) dissolved in 20 mL of ethanol was added 50 mg of 10% palladium on carbon. The flask was fitted with a three-way stopcock connected to a hydrogen-filled balloon and a nitrogen/vacuum manifold. The flask was evacuated, filled with nitrogen, evacuated again, and then put under a hydrogen atmosphere. The mixture was stirred at ambient temperature for 14 hours. The hydrogen was evacuated and the flask filled with nitrogen. The catalyst was removed by filtration through a pad of Celite® and the solvent removed *in vacuo*. The crude product was purified by preparative HPLC (Vydac µC18) eluting with a 10-70% gradient of CH_3CN in 0.1% TFA. The appropriate fraction was lyophilized to give the product as a white solid (34.7 mg, 62 %). ^1H NMR (CD_3OD, 300 MHz) of major tautomer δ 0.75 (d, 3H, J=7Hz), 0.78 (d, 3H, J=7Hz), 1.1-1.4 (m, 8H), 1.5-1.9 (m, 6H), 2.53 (s, 3H), 3.33 (m, 1H), 3.50 (m, 2H), 3.77 (s,3H), 4.03 (t, 1H, J=8Hz), 5.40(dd, 1H, J=6Hz,10Hz), 7.04 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.06 (s, 1H),7.18 (ddd

1H, J=1Hz,7Hz,8Hz), 7.35 (d, 1H, J=8Hz), 7.47 (d, 1H, J=8Hz). MS (FAB/NBA) m/e 599 $(M+Cu)^+$. Anal calcd for $C_{29}H_{40}N_6O_4 \cdot 1.7$ TFA: C, 53.27; H, 5.75; N, 11.50. Found: C, 53.25; H, 6.01; N, 11.77.

Example 28

2-{(1R)-1-[N-(*endo*-2-Norbornylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid

The title compound was prepared according to the procedures described in Example 27 but substituting *endo*-2-norbornylamine for cyclohexylamine in Example 27D. The crude material was purified by preparative HPLC (Vydac μC18) eluting with a 0-80% gradient of CH_3CN in 0.1% TFA. The desired fractions were lyophilized to give the title compound as a white solid (29 mg). ^1H NMR (CD_3OD, 300 MHz) of one diastereomer δ 0.76 (d, 3H, J=6Hz), 0.78 (d, 3H, J=6Hz), 1.2-1.6 (m, 10H), 2.00 (m, 1H), 2.17 (m, 1H), 2.34 (m, 1H), 2.51 (s, 3H), 3.32 (dd, 1H, J=10,15Hz), 3.55 (dd, 1H, J=6,15Hz), 3.76 (s, 3H), 3.91 (m, 1H), 4.03 (dt, 1H, J=3,7Hz), 5.38 (ddd, 1H, J=3,7,9Hz), 7.04 (ddd, 1H, J=1,7,8Hz), 7.06 (s, 1H), 7.18 (dt, 1H, J=1,7Hz), 7.35 (d, 1H, J=8Hz), 7.46 (d, 1H, J=8Hz). MS (FAB/NBA) m/e 549 $(M+H)^+$. Anal calcd for $C_{30}H_{40}N_6O_4 \cdot 1.6$ TFA: C, 54.54; H, 5.74; N, 11.49. Found: C, 54.21; H, 5.76; N, 11.57.

Example 29

2-{(1R)-1-[N-(*exo*-2-Norbornylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid

The title compound was prepared according to the procedures described in Example 27 but substituting *exo*-2-norbornylamine for cyclohexylamine in Example 27D. The crude material was purified by preparative HPLC (Vydac μC18) eluting with a 0-80% gradient of CH_3CN in 0.1% TFA. The desired fractions were lyophilized to give the title compound as a white solid (45 mg). ^1H NMR (CD_3OD, 300 MHz) of one diastereomer δ 0.75 (d, 3H, J=6Hz), 0.77 (d, 3H, J=6Hz), 1.1-1.5 (m, 10H), 1.70 (m, 1H), 2.13 (m, 1H), 2.24 (m, 1H), 2.53 (s, 3H), 3.33 (dd,

1H, J=10,15Hz), 3.49 (m, 1H), 3.57 (m, 1H), 3.77 (s, 3H), 4.02 (dt, 1H, J=1,7Hz), 5.39 (ddd, 1H, J=2,6,8Hz), 7.04 (dt, 1H, J=1,7Hz), 7.06 (s, 1H), 7.17 (dt, 1H, J=1,7Hz), 7.35 (d, 1H, J=8Hz), 7.46 (d, 1H, J=8Hz). MS (FAB/NBA) m/e 549 $(M+H)^+$. Anal calcd for $C_{30}H_{40}N_6O_4 \cdot 1.9$ TFA: C, 53.05; H, 5.52; N, 10.98. Found: C, 52.77; H, 5.97; N, 11.46.

Example 30

2-{(1R)-1-[N-(*trans*-4-Hydroxycyclohexylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid

The title compound was prepared according to the procedures described in Example 27 but substituting *trans*-4-hydroxycyclohexylamine for cyclohexylamine in Example 27D. The crude material was purified by preparative HPLC (Vydac μC18) eluting with a 0-80% gradient of CH_3CN in 0.1% TFA. The desired fractions were lyophilized to give the title compound as a white solid (18 mg). ^1H NMR (CD_3OD, 300 MHz) of major tautomer δ 0.75 (d, 3H, J=6Hz), 0.77 (d, 3H, J=6Hz), 1.1-1.4 (m, 7H), 1.8-2.0 (m, 4H), 2.52 (s, 3H), 3.33 (dd, 1H, J=12,15Hz), 3.49 (m, 2H), 3.56 (dd, 1H, J=7,15Hz), 3.77 (s, 3H), 4.03 (t, 1H, J=7Hz), 5.40 (dd, 1H, J=6,9Hz), 7.04 (dt, 1H, J=1,7Hz), 7.06 (s, 1H), 7.17 (dt, 1H, J=1,7Hz), 7.35 (d, 1H, J=8Hz), 7.47 (d, 1H, J=8Hz). MS (FAB/NBA) m/e 553 $(M+H)^+$. Anal calcd for $C_{29}H_{40}N_6O_5 \cdot 1.5$ TFA: C, 53.11; H, 5.78; N, 11.61. Found: C, 52.98; H, 6.03; N, 11.74.

Example 31

2-{(1R)-1-[N-(2-Methylcyclohexylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-imidazole-4-carboxylic acid

The title compound was prepared according to the procedures described in Example 27 but substituting 2-methylcyclohexylamine (mixture of *cis* and *trans*) for cyclohexylamine in Example 27D. The crude material was purified by preparative HPLC (Vydac μC18) eluting with a 0-80% gradient of CH_3CN in 0.1% TFA. The desired fractions were lyophilized to give the title compound as a white solid. ^1H NMR (CD_3OD, 300 MHz) consistent with structure of the four isomers δ 2.50

(s, 3H), 3.77 (s, 3H), 7.03 (t, 1H, J=8Hz), 7.06 (s, 1H), 7.17 (t, 1H, J=8Hz), 7.33 (d, 1H, J=8Hz), 7.48 (d, J=8Hz). MS (FAB/NBA) m/e 551 $(M+H)^+$. Anal calcd for $C_{30}H_{42}N_6O_4 \cdot 1.6$ TFA: C, 54.39; H, 5.99; N, 11.46. Found: C, 54.54; H, 6.24; N, 11.39.

Example 32

2-[(1R)-1-[N-(3-Methylcyclohexylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-imidazole-4-carboxylic acid

The title compound was prepared according to the procedures described in Example 27 but substituting 3-methylcyclohexylamine (mixture of *cis* and *trans*) for cyclohexylamine in Example 27D. The crude material was purified by preparative HPLC (Vydac μC18) eluting with a 0-80% gradient of CH_3CN in 0.1% TFA. The desired fractions were lyophilized to give the title compound as a white solid. ^1H NMR (CD_3OD, 300 MHz) consistent with structure of the four isomers δ 2.50 (s, 3H), 3.76 (s, 3H), 7.0 (t, 1H, J=8Hz), 7.03 (s, 1H), 7.16 (t, 1H, J=8Hz), 7.32 (d, 1H, J=8Hz), 7.50 (d, J=8Hz). MS (FAB/NBA) m/e 551 $(M+H)^+$. Anal calcd for $C_{30}H_{42}N_6O_4 \cdot 1.5$ TFA: C, 54.92; H, 6.08; N, 11.64. Found: C, 55.08; H, 6.20; N, 11.70.

Example 33

2-[(1R)-1-[N-(4-Methylcyclohexylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-imidazole-4-carboxylic acid

The title compound was prepared according to the procedures described in Example 27 but substituting 4-methylcyclohexylamine (mixture of *cis* and *trans*) for cyclohexylamine in Example 27D. The crude material was purified by preparative HPLC (Vydac μC18) eluting with a 0-80% gradient of CH_3CN in 0.1% TFA. The desired fractions were lyophilized to give the title compound as a white solid (28 mg). ^1H NMR (CD_3OD, 300 MHz) of mixture δ 0.76 (m, 6H), 0.91 (apparent t, 3H), 1.0-1.9 (m, 12H), major isomer 2.52 (s, 3H), 3.33 (m, 1H), 3.56 (dd, 1H, J=7,15Hz), 3.76 (s, 3H), 3.78 (m, 1H), 4.03 (m, 1H), 5.20 (dd, 1H, J=6,9Hz), 7.04 (dt, 1H, J=1,7Hz), 7.05 (s, 1H), 7.18 (dt, 1H, J=1,7Hz),

7.35 (d, 1H, J=8Hz), 7.47 (d, 1H, J=8Hz). MS (DCI/NH_3) m/e 551 $(M+H)^+$. Anal calcd for $C_{30}H_{42}N_6O_4 \cdot 1.1$ TFA: C, 57.20; H, 6.43; N, 12.43. Found: C, 57.27; H, 6.45; N, 12.30.

Example 34

2-[(1R)-1-[(N-Cyclopentylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-imidazole-4-carboxylic acid

The title compound was prepared according to the procedures described in Example 27 but substituting cyclopentylamine for cyclohexylamine in Example 27D. The crude material was purified by preparative HPLC (Vydac μC18) eluting with a 0-80% gradient of CH_3CN in 0.1% TFA. The desired fractions were lyophilized to give the title compound as a white solid. ^1H NMR (CD_3OD, 300 MHz) of major tautomer δ 0.72 (d, 3H, J=7Hz), 0.75 (d, 3H, J=7Hz), 1.1-1.5 (m, 6H), 1.5-1.8 (m, 5H), 2.48 (s, 3H), 2.72 (s, 3H), 3.18 (m, 1H), 3.58 (m, 2H), 3.72 (s,3H), 4.05 (t, 1H, J=8Hz), 5.36(dd, 1H, J=6Hz,10Hz), 6.95 (s, 1H), 7.0 (t, 1H, J=8Hz), 7.15 (t, 1H, J=8Hz), 7.30 (d, 1H, J=8Hz), 7.54 (d, 1H, J=8Hz). MS (DCI) m/e 523 $(M+H)^+$. Anal calcd for $C_{28}H_{38}N_6O_4 \cdot 1.55$ H_2O, 1.10 TFA: C, 53.66; H, 6.29 N, 12.43. Found: C, 53.96; H, 6.55; N, 12.04.

Example 35

2-[(1R)-1-[(N-Cycloheptylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-imidazole-4-carboxylic acid

The title compound was prepared according to the procedures described in Example 27 but substituting cycloheptylamine for cyclohexylamine in Example 27D. The crude material was purified by preparative HPLC (Vydac μC18) eluting with a 0-80% gradient of CH_3CN in 0.1% TFA. The desired fractions were lyophilized to give the title compound as a white solid. ^1H NMR (CD_3OD, 300 MHz) of major tautomer δ 0.72 (d, 3H, J=7Hz), 0.75 (d, 3H, J=7Hz), 1.1-1.5 (m, 10H), 1.5-1.8 (m, 5H), 2.48 (s, 3H), 2.72 (s, 3H), 3.18 (m, 1H), 3.58 (m, 2H), 3.72 (s,3H), 4.05 (t, 1H, J=8Hz), 5.36(dd, 1H, J=6Hz,10Hz), 6.95 (s, 1H),

7.0 (t, 1H, J=8Hz), 7.15 (t, 1H, J=8Hz), 7.30 (d, 1H, J=8Hz), 7.54 (d, 1H, J=8Hz). MS (ESI) m/e 551 $(M+H)^+$. Anal calcd for $C_{30}H_{42}N_6O_4 \cdot 1.5\ H_2O$, 0.5 TFA: C, 58.66; H, 7.23; N, 13.24. Found: C, 58.35; H, 7.35; N, 13.45.

Example 36

2-[(1R)-1-[N-(N-Cyclohexyl-N-methylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-imidazole-4-carboxylic acid

The title compound was prepared according to the procedures described in Example 27 but substituting N-methylcyclohexylamine for cyclohexylamine. The crude product was triturated with 50% diethyl ether/hexane, dissolved in acetonitrile and water and then lyophilized. ^1H NMR (CD_3OD, 300 MHz) of major tautomer δ 0.72 (d, 3H, J=7Hz), 0.75 (d, 3H, J=7Hz), 1.1-1.5 (m, 8H), 1.5-1.8 (m, 5H), 2.48 (s, 3H), 2.72 (s, 3H), 3.18 (m, 1H), 3.58 (m, 2H), 3.72 (s,3H), 4.05 (t, 1H, J=8Hz), 5.36(dd, 1H, J=6Hz,10Hz), 6.95 (s, 1H), 7.0 (t, 1H, J=8Hz), 7.15 (t, 1H, J=8Hz), 7.30 (d, 1H, J=8Hz), 7.54 (d, 1H, J=8Hz). MS (FAB/NBA) m/e 551 $(M+H)^+$. Anal calcd for $C_{30}H_{42}N_6O_4 \cdot 2\ H_2O$: C, 61.41; H, 7.90; N, 14.32. Found: C, 61.60; H, 7.77; N, 14.33.

Example 37

2-[(1R)-1-[(N-Cyclohexylaminocarbonyl)-Leucyl-amino]-2-(1-ethyl-indol-3-yl)ethyl]-5-methyl-imidazole-4-carboxylic acid

The title compound was prepared according to the procedures described in Example 27 but substituting Fmoc-D-(1-ethyl)Tryptophan for Fmoc-D-(1-methyl)Tryptophan in Example 1A. The crude product was purified by preparative HPLC (Vydac μC18) eluting with a 10-70% gradient of CH_3CN in 0.1% TFA. The appropriate fraction was lyophilized to give the product as a white solid. MS (DCI/NH_3) m/e 551 $(M+H)^+$.

Example 38

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-imidazole-4,5-dicarboxylic acid

The title compound was prepared by the procedures described in Example 1 but substituting trifluoroacetyl chloride for acetyl chloride in Example 1A. Saponification of the ethyl ester gives the dicarboxylic acid through concomitant hydrolysis of the trifluoromethyl group. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.94 (d, 3H, J=6Hz), 0.97 (d, 3H, J=7Hz), 1.3-1.4 (m, 2H), 1.49 (m, 5H), 1.67 (m, 4H), 3.3-3.6 (m, 6H), 4.35 (dd, 1H, J=5Hz,10Hz), 5.39 (t, 1H, J=8Hz), 6.98 (dt, 1H, J=1Hz,8Hz), 7.06 (s, 1H), 7.10 (dt, 1H, J=1Hz,8Hz), 7.36 (d, 1H, J=8Hz), 7.42 (d, 1H, J=8Hz). MS (DCI/NH_3) m/e 553(M+H)$^+$. HRMS Calcd for $C_{28}H_{37}N_6O_6$: 553.2775. Found: 553.2772.

Example 39

2-{2R-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-3-(indol-3-yl)propyl}-5-methyl-imidazole-4-carboxylic acid

Example 39A

Cbz-α-homo-D-Tryptophan

Cbz-D-Tryptophan (2.69 g, 8.1 mmol) was dissolved in THF (50 mL) and cooled to -20 °C. N-methylmorpholine (0.9 mL, 8.1 mmol) and isobutyl chloroformate (1.05 mL, 8.1 mmol) were added. The slurry was stirred at -20 °C for 40 minutes, and then filtered through Celite® to remove the precipitate. The Celite® was washed with ice cold THF.

Ethereal diazomethane (250 mL of ~0.3 N solution) was cooled to -20 °C in a 500-mL clearseal round-bottom flask. The above mixed anhydride solution was added dropwise over 15 minutes. After 15 minutes of additional stirring, the bath was removed and the solution allowed to warm to ambient temperature over 150 minutes. The solvents were removed *in vacuo*; and the residue was taken up in EtOAc and washed with water and brine. The organic phase was dried over Na_2SO_4 and evaporated *in vacuo*. The crude product was dissolved in

methanol (100 mL). A solution of silver benzoate (1.0 g) in triethylamine(10 mL) (filtered through a short pad of Celite®) was added over a 5 minute period. After stirring for 60 minutes the solution turned dark brown. The solvents were removed *in vacuo*; and the residue was stirred with 120 mL of a 1:1 water-ethyl acetate mixture for 10 minutes and then filtered through a pad of Celite®. The organic layer was washed with brine, dried over Na_2SO_4 and evaporated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with a gradient of 3:1 going to 1:1 hexanes-ethyl acetate to elute the product (2.63 g, 89% yield) as a colorless oil.

A portion of the above material (1.10 g, 3.0 mmol) was dissolved in THF (15 mL). A solution of LiOH (0.15 g) in water (5 mL) was added. The mixture was stirred at ambient temperature for 3 hours, and then heated to 40 °C for 2 hours. The organic solvent was removed *in vacuo*; the solution was neutralized with 1 N H_3PO_4 and extracted with EtOAc to give the crude acid, which was used without further purification.

Example 39B

2-{2R-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-3-(indol-3-yl)propyl}-5-methyl-imidazole-4-carboxylic acid

The title compound was prepared by the procedures described in Example 1 but substituting the compound resulting from Example 39A in Example 1A. ^1H NMR of major tautomer (CD_3OD, 300 MHz) δ 0.77 (d, 3H, J=6Hz), 0.80 (d, 3H, J=6Hz), 1.15-1.3 (m, 2H), 1.54 (m, 4H), 1.69 (m, 5H), 2.49 (s, 3H), 2.95 (dd, 1H, J=9Hz,15Hz), 3.07 (m, 2H), 3.2-3.5 (m, 5H), 4.02 (dd, 1H, J=6Hz,9Hz), 4.62 (m, 1H), 7.01 (dt, 1H, J=1Hz,8Hz), 7.09 (dt, 1H, J=1Hz,8Hz), 7.09 (s, 1H), 7.32 (d, 1H, J=8Hz), 7.56 (d, 1H, J=8Hz). MS (FAB+NBA) m/e 537 $(M+H)^+$. HRMS Calcd. for $C_{29}H_{41}N_6O_4$: 537.3189. Found: 537.3192 .

Example 40

2-{(1R)-1-[N-(N-(Homopiperidin-1-ylcarbonyl)-Leucyl)-N-methylamino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid

Example 40A

Cbz-D-(N_{α},Ni-dimethyl)-Tryptophan.

Sodium hydride (1.8 g, 60 mmol, 80% oil dispersion, washed twice with hexanes) was suspended in THF (25 mL) and cooled to 0 °C. A solution of Cbz-D-Tryptophan (5.4 g, 16 mmol) in THF (25 mL) was added over 10 minutes. After gas evolution ceased, four 2-mL portions of methyl iodide were added over 10 minutes. The bath was removed, and the mixture allowed to warm to ambient temperature over 3 hours. The mixture was transferred slowly into an ice cold 3% citric acid solution. The volatile organics were removed *in vacuo*, EtOAc (50 mL) was added, and the aqueous phase was decanted. The organics were extracted with 0.25 N NaOH (100 mL). The aqueous extract was acidified with 1 N H_3PO_4 and extracted twice with EtOAc. The organic extracts were washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4, and concentrated *in vacuo* to afford the crude product, which was used without further purification.

Example 40B

2-{(1R)-1-[N-(N-(Homopiperidin-1-ylcarbonyl)-Leucyl)-N-methylamino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid

The title compound was prepared by the methods described in Example 1 but substituting the compound resulting from Example 40A for Cbz-D-tryptophan in Example 1A. The crude material was purified by preparative HPLC (Vydac μC18) eluting with a 0-80% gradient of CH_3CN in 0.1% TFA. The desired fractions were lyophilized to give the title compound as a white solid (17 mg). ^1H NMR (CD_3OD, 300 MHz) of major tautomer δ 0.63 (d, 3H, J=6Hz), 0.65 (d, 3H, J=6Hz), 1.45-1.6 (m, 5H), 1.6-1.8 (m, 6H), 2.63 (s, 3H), 3.00 (s, 3H), 3.43 (m, 4H), 3.50 (dd, 1H, J=12,15Hz), 3.68 (dt, 1H, J=5,12Hz), 3.77 (s, 3H), 4.36 (dt, 1H,

J=5,10Hz), 6.38 (dd, 1H, J=5,12Hz), 7.07 (ddd, 1H, J=1,7,8Hz), 7.12 (s, 1H), 7.19 (dt, 1H, J=1,7Hz), 7.35 (d, 1H, J=8Hz), 7.63 (d, 1H, J=8Hz). MS (FAB/MeOH) m/e 551 $(M+H)^+$, 573 $(M+Na)^+$. Anal calcd for $C_{30}H_{42}N_6O_4 \cdot 2.0$ TFA: C, 52.44; H, 5.70; N, 10.79. Found: C, 51.97; H, 5.70; N, 10.79. HRMS calcd for $C_{30}H_{43}N_6O_4$: 551.3346. Found: 551.3332.

Example 41

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-imidazole-4-carboxylic acid

Example 41A

Boc-D-(1-methyl)-Tryptophanyl-$CSNH_2$

Boc-D-Trp(Me)-OH (0.955 g, 3.0 mmol) was dissolved in THF (25 mL) and cooled to -20 °C. N-Methylmorpholine (0.33 mL, 1.0 eq) and isobutyl chloroformate (0.39 mL, 1.0 eq) were added and the slurry stirred for 30 minutes at which time a solution of concentrated ammonia (0.2 mL) in THF (3 mL) was added. The mixture was warmed slowly to 0 °C over 1 hour. The solvents were removed *in vacuo*, and the residue was taken up in ethyl acetate, washed with water, saturated sodium bicarbonate solution, 1N H_3PO_4 and brine, dried, and concentrated *in vacuo* to give 0.95 g (100% yield) of the amide as a white foam.

Boc-D-(1-methyl)-Tryptophanyl amide (0.50 g, 1.57 mmol) was dissolved in THF (10 mL) and Lawesson's reagent (770 mg, 1.90 mmol, 1.2 eq) was added. The solution was stirred at ambient temperature for 65 hours. The solvents were removed *in vacuo*, and the residue was taken up in EtOAc and washed with 1:1 saturated sodium bicarbonate solution/water and brine. The organic phase was dried over Na_2SO_4 and evaporated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with 2:1 hexanes-ethyl acetate to give the product (442 mg, 86% yield) as a light yellow foam.

Example 41B

Boc-D-(1-methyl)-Tryptophanyl-C(=NH)NH_2

The thioamide resulting from Example 41A (400 mg, 1.22 mmol) was dissolved in THF (2 mL) and added to a Carius tube. The tube was purged with nitrogen and cooled to -78 °C. Ammonia (2 mL) was condensed into the tube. The tube was sealed, allowed to warm to ambient temperature, and stirred for 6 days during which time a white solid formed. The solvents were removed *in vacuo*; the residue was taken up in ether and filtered. The filtrate was washed twice with diethyl ether to give 260 mg (68% yield) of the title compound as a white solid.

Example 41C

2-{(1R)-1-(Boc-Amino)-2-(1-methyl-indol-3-yl)ethyl}-imidazole-4-carboxylic acid ethyl ester

The amidine resulting from Example 41B (130 mg, 0.41 mmol) was combined in THF (2 mL) with ethyl bromopyruvate (88 mg, 0.45 mmol, 1.1 eq) and propylene oxide (29 mg, 0.5 mmol). The solution was stirred overnight at ambient temperature and the solvents removed *in vacuo*. The crude product was taken up in pyridine (2 mL) and methanesulfonyl chloride (7 drops) and triethylamine (5 drops) were added. The mixture was heated at 80 °C for 5 hours. The solvents were removed *in vacuo*, and the residue was taken up in EtOAc and washed with 1:1 saturated sodium bicarbonate/water, 1 N H_3PO_4 and brine. The organic phase was dried over Na_2SO_4 and evaporated *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with 2:1 hexanes-ethyl acetate to give the product (35 mg, 21% yield) as a yellow oil.

Example 41D

2-[(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-imidazole-4-carboxylic acid

The compound resulting from Example 41C (35 mg) was dissolved in trifluoroacetic acid (3 mL) and stirred at ambient temperature for 45 minutes. The solvents were removed *in vacuo*, and the residue was taken up in saturated sodium bicarbonate solution and extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 and evaporated *in vacuo* to give the crude product as a yellow solid which was dissolved in THF (5 mL). HOBt (13 mg), N-(homopiperidin-1-ylcarbonyl)-leucine (25 mg), prepared in Example 1D, and EDCI (20 mg) were added. N-Methylmorpholine (10 µL) and DMF (1 mL) were added and the mixture stirred at room temperature for 18 hours. The solvent was evaporated under reduced pressure and the residue taken up in EtOAc. The solution was washed with saturated $NaHCO_3$ solution, 1 N H_3PO_4 and brine, dried with $MgSO_4$, and evaporated *in vacuo* to give yellow oil which was purified by flash chromatography on silica gel eluting with 50% EtOAc-hexane. The product was dissolved in THF (2 mL) and a solution of LiOH (50 mg) in H_2O (1 mL) was added. The mixture was heated in a Carius tube at 110 °C for 15 hours. The solvents were evaporated under reduced pressure and the residue purified by preparative HPLC (Vydac µC18) eluting with a 0-70% gradient of CH_3CN in 0.1% TFA. The desired fractions were lyophilized to give the title compound as a white solid. ^1H NMR (CD_3OD, 300 MHz) δ 0.80 (d, 6H, J=7Hz), 1.4 (m, 2H), 1.52 (m, 5H), 1.67 (m, 4H), 3.3-3.6 (m, 6H), 3.74 (s, 3H), 4.34 (dd, 1H, J=7Hz,9Hz), 5.56 (dd, 1H, J=5Hz,8Hz), 6.96 (s, 1H), 7.02 (dt, 1H, J=1Hz,8Hz), 7.14 (dt, 1H, J=1Hz,8Hz), 7.30 (d, 1H, J=8Hz), 7.52 (d, 1H, J=8Hz), 8.24 (s, 1H). MS (DCI/NH_3) m/e 540 $(M+NH_4)^+$, 557 $(M+NH_4+NH_3)^+$.

Example 42

2-[(1R)-1-[N-(Cyclohexyloxycarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-imidazole-4-carboxylic acid

Example 42A

1-(Cyclohexyloxycarbonyl)-Leucine

Cyclohexanol (0.53 mL) was dissolved in THF (10 mL) and cooled to 0 °C. Phosgene (2.6 mL, 1.97 M in toluene) was added and the solution stirred for 90 minutes. A solution of Leu-OBn · TsOH (1.97 g) and Et_3N (0.8 mL) in THF (20 mL) was added slowly over 5 minutes, followed by additional Et_3N (0.8 mL). The mixture was allowed to warm to ambient temperature over 2 hours. The solvents were removed *in vacuo*; and the residue was taken up in EtOAc and washed with 1:1 saturated sodium bicarbonate solution/water, 1 N H_3PO_4 and brine. The organic phase was dried over Na_2SO_4, filtered through Celite®, and concentrated to give a yellow oil, which was purified by flash chromatography eluting with 6:1 hexanes-EtOAc. The product was dissolved in ethanol (50 mL), 10% palladium on carbon (100 mg) was added, and the mixture was purged with nitrogen. The nitrogen line was exchanged for a balloon of hydrogen, and the mixture was stirred at ambient temperature for 4 hours. The catalyst was removed by filtration through Celite®. The solvents were removed *in vacuo* to give the title compound as a white solid.

Example 42B

2-[(1R)-1-[N-(Cyclohexyloxycarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-imidazole-4-carboxylic acid

The title compound was prepared according to the procedures described in Example 27 but substituting the compound resulting from Example 42A for N-(cyclohexylaminocarbonyl)-Leucine in Example 27E. The crude material was purified by trituration with ether-EtOAc to give a white solid which was dissolved in 0.1% aqueous TFA in acetonitrile and lyophilized to give a white powder (106 mg). ^1H NMR

(CD_3OD, 300 MHz) of major tautomer δ 0.78 (d, 3H, J=6Hz), 0.81 (d, 3H, J=6Hz), 1.2-1.9 (m, 13H), 2.45 (s, 3H), 3.3-3.5 (m, 2H), 3.76 (s, 3H), 4.02 (m, 1H), 4.59 (m, 1H), 5.23 (t, 1H, J=8Hz), 7.03 (dt, 1H, J=1,7Hz), 7.04 (s, 1H), 7.17 (dt, 1H, J=1,7Hz), 7.33 (d, 1H, J=8Hz), 7.45 (d, 1H, J=8Hz). MS (FAB/NBA) m/e 538 $(M+H)^+$, 560 $(M+Na)^+$. Anal calcd for $C_{29}H_{39}N_5O_5 \cdot 1.3$ TFA: C, 55.34; H, 5.92; N, 10.21. Found: C, 55.35; H, 5.92; N, 10.24.

Example 43

2-[(1R)-1-[N-(Phenylaminocarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl]-5-methyl-imidazole-4-carboxylic acid

Example 43A

N-(Phenylaminocarbonyl)-leucine

Leu-OBn · p-TsOH (2.0 g) was suspended in THF (5 mL). N-Methyl morpholine (0.56 mL, 0.51 g) and phenyl isocyanate (0.55 mL, 0.6 g) were added and the solution stirred at ambient temperature for four hours. The solvent was evaporated and the residue dissolved in EtOAc (20 mL). The solution was washed with saturated $NaHCO_3$ solution, 1 N H_3PO_4 and brine, dried with $MgSO_4$, and evaporated under reduced pressure to give a colorless oil which was dissolved in EtOH (25 mL). 10% Palladium on carbon (200 mg) was added. The flask was fitted with a three-way stopcock connected to a hydrogen-filled balloon and a nitrogen/vacuum manifold. The flask was evacuated, filled with nitrogen, evacuated again, and then put under a hydrogen atmosphere. The mixture was stirred at ambient temperature for 14 hours. The hydrogen was evacuated and the flask filled with nitrogen. The catalyst was removed by filtration through a pad of Celite® and the solvent removed *in vacuo* to give a colorless oil which solidified on standing (1.08 g, 85% yield).

Example 43B

2-[(1R)-1-[N-(Phenylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-imidazole-4-carboxylic acid

The title compound was prepared by the procedures described in Example 27 but substituting the compound resulting from Example 43A for N-(cyclohexylaminocarbonyl)-Leucine in Example 27E. The crude material was purified by trituration with ether/EtOAc to give a white solid which was dissolved in 0.1% aqueous TFA in acetonitrile and lyophilized to give the title compound (25 mg). ^{1}H NMR (CD_3OD, 300 MHz) of major tautomer δ 0.80 (d, 3H, J=7Hz), 0.81(d, 3H, J=7Hz), 1.34 (m, 3H), 2.43 (s, 3H), 3.33 (dd, 1H, J=9,14Hz), 3.54 (dd, 1H, J=6,14Hz), 3.72 (s, 3H), 4.14 (m, 1H), 5.38 (dd, 1H, J=6,9Hz), 7.00 (dt, 1H, J=1,7Hz), 7.03 (dt, 1H, J=1,8Hz), 7.05 (s, 1H), 7.16 (dt, 1H, J=1,7Hz), 7.26 (m, 1H), 7.28 (d, 1H, J=8Hz), 7.31 (m, 3H), 7.45 (d, 1H, J=8Hz). MS (FAB/NBA) m/e 531 $(M+H)^+$, 553 $(M+Na)^+$. Anal calcd for $C_{29}H_{34}N_6O_4 \cdot 1.5$ TFA: C, 54.78; H, 5.10; N, 11.98. Found: C, 54.80; H, 5.29; N, 12.11.

Example 44

2-[(1R)-1-[N-(N-Cyclohexylaminocarbonyl-N-methyl-Leucyl)-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-imidazole-4-carboxylic acid

N-Boc-N-methyl-Leu-OH (85mg), prepared by the method of Cheung and Benoiton, Can. J. Chem. 55 906 (1977), was dissolved in THF (4 mL) and DMF (2 mL). 2-[(1R)-1-Amino-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-imidazole-4-carboxylic acid benzyl ester (63 mg), prepared according to the procedures described in Example 27C, HOBt (42 mg), N-methylmorpholine (8 drops), and EDCI (57 mg) were added and the mixture stirred at ambient temperature for 18 hours. The solvent was evaporated, the residue taken up in EtOAc, washed with saturated sodium bicarbonate solution, 1 N H_3PO_4, and brine, and evaporated to give a yellow oil which was dissolved in TFA (5 mL). The solution was stirred at ambient temperature for two hours. The solvent was evaporated and the residue taken up in saturated sodium bicarbonate solution and extracted with EtOAc. The organic layer was washed with

brine and evaporated. The crude product was dissolved in THF (5 mL). N-Methylmorpholine (0.2 mL) and cyclohexylisocyanate (5 drops) were added and the solution stirred at ambient temperature for 18 hours. The solvent was evaporated, the residue taken up in EtOAc, washed with saturated sodium bicarbonate solution, 1 N H_3PO_4, and brine, and evaporated to give a yellow oil which was dissolved in EtOH (20 mL). 10% palladium on carbon (30 mg) was added and the mixture was purged with nitrogen. The nitrogen line was exchanged for a balloon of hydrogen, and the mixture was stirred at ambient temperature for 4 hours. The catalyst was removed by filtration through Celite® and the solvents evaporated. The crude product was triturated with 1:1 EtOAc-ether to give a white solid which was dissolved in 0.1% aqueous TFA in acetonitrile and lyophilized to give the title compound as a white powder (30 mg). ^1H NMR (CD_3OD, 300 MHz) of major tautomer δ 0.86 (d, 3H, J=7Hz), 0.89 (d, 3H, J=7Hz), 1.0-1.8 (m, 13H), 2.48 (s, 3H), 2.72 (s, 3H), 3.3-3.5 (m, 3H), 3.75 (s, 3H), 4.51 (dd, 1H, J=7,10Hz), 5.29 (t, 1H, J=7Hz), 7.02 (s, 1H), 7.04 (dt, 1H, J=1,7Hz), 7.18 (dt, 1H, J=1,7Hz), 7.35 (d, 2H, J=8Hz). MS (DCI/NH_3) m/e 551 $(M+H)^+$. HRMS calcd for $C_{30}H_{43}N_6O_4$: 551.3346. Found: 551.3351.

Example 45

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-thiazole-4-carboxylic acid

Example 45A

Cbz-D-Tryptophanyl-(2-acetylGlycine) ethyl ester

N-(Diphenylmethylene)glycine ethyl ester (30.0 g) was dissolved in THF (125 mL) and the solution cooled to -78 °C. Lithium hexamethyldisilazide (100 mL, 1 N solution in THF) was added slowly over 10 minutes, and the resulting yellow slurry was stirred at -78 °C for 45 minutes. The slurry was then transferred via cannula to a solution of acetyl chloride (8.4 mL) in THF (50 mL) at -78 °C. Additional THF (250 mL) was added to the anion solution to facilitate transfer to the acetyl

chloride solution. Complete transfer of the anion took about 2.5 hours. After the addition was complete, the reaction was allowed to warm to room temperature and stirring was continued for four hours. The reaction was then quenched with 2 N HCl (115 mL). The THF was evaporated and the resulting aqueous solution was washed with EtOAc (2 x 100 mL). The organic phases were discarded and the aqueous phase was concentrated *in vacuo*. The resulting slurry was treated with EtOH (150 mL) and the insolubles filtered off. The filtrate was evaporated to give 2-acetylglycine ethyl ester hydrochloride as a yellow solid which was used without further purification.

Cbz-D-Tryptophan (40.6 g) was dissolved in THF (100 mL) and the solution cooled to -20 °C. N-Methylmorpholine (13 mL) was added followed by the dropwise addition of isobutylchloroformate (15.6 mL). After the addition was complete, the reaction was stirred for 30 minutes at -20 °C at which time the bath was removed. The 2-acetylglycine ester from above was dissolved in DMF (50 mL) and added to the mixed anhydride. N-Methylmorpholine (13 mL) was then added via syringe pump over a one hour period. After the addition was complete, the reaction was allowed to stir at room temperature for one hour. Water (200 mL) was added and the layers separated. The organic layer was washed with saturated $NaHCO_3$ solution, 1 N H_3PO_4 and brine, dried with $MgSO_4$, and evaporated under reduced pressure to give an orange oil which was purified by flash chromatography on silica gel eluting with 15% EtOAc-hexane. The title compound was isolated as an orange oil (30.7 g, 59% yield for the two steps). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.26 (dt, 3H, J=1Hz,7Hz), 2.24 (s, 1.5H), 2.30 (s, 1.5H), 3.20 (m, 1H), 3.35 (m, 1H), 4.22 (dq, 2H, J=1Hz,7Hz), 4.50 (m, 1H), 5.06 (dd, 1H, J=7Hz,8Hz), 5.12 (s, 2H), 5.45 (m, 1H), 6.82 (m, 1H), 7.23 (m, 9H), 7.65 (m, 1H), 8.10 (s, 1H). MS (DCI/NH_3) m/e 466 $(M+H)^+$, 483 $(M+NH_4)^+$.

Example 45B

2-{(1R)-(Cbz-Amino)-2-(indol-3-yl)ethyl}-5-methyl-thiazole-4-carboxylic acid ethyl ester

The compound resulting from Example 45A (0.335 g) was dissolved in THF (5 mL). Lawesson's reagent (0.45 g) was added and the mixture stirred at reflux for five hours. The solvent was evaporated under reduced pressure and the residue taken up in EtOAc (20 mL). The solution was washed with saturated $NaHCO_3$ solution, 1 N H_3PO_4 and brine, dried with $MgSO_4$ and evaporated under reduced pressure to give a yellow oil which was purified by flash chromatography eluting with 15% EtOAc-hexane to give the product as a white solid (155 mg, 46%). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.43 (t, 3H, J=7Hz), 2.65 (s, 3H), 3.42 (m, 1H), 3.55 (m, 1H), 4.43 (q, 2H, J=7Hz), 5.09 (s, 2H), 5.38 (m, 1H), 5.63 (br s, 1H), 6.90 (s, 1H), 7.07(t, 1H, J=8Hz), 7.18 (t, 1H, J=8Hz), 7.32 (m, 6H), 7.52 (1H, d, J=8Hz), 8.01 (s, 1H). MS (DCI/NH_3) m/e 464 $(M+H)^+$, 481 $(M+NH_4)^+$.

Example 45C

2-{(1R)-Amino-2-(indol-3-yl)ethyl}-5-methyl-thiazole-4-carboxylic acid ethyl ester

The compound resulting from Example 45B (72 mg, 0.15 mmol) was dissolved in 2 mL of 30% HBr in HOAc and stirred at ambient temperature for 3 hours. The solvents were removed *in vacuo*; the residue was taken up in saturated sodium bicarbonate solution and extracted with EtOAc. The combined organic extracts were washed with brine and dried over Na_2SO_4. The solvents were removed *in vacuo*, and the crude product was used directly for subsequent coupling reactions.

Example 45D

N-(Homopiperidin-1-ylcarbonyl)-Leucyl-OH

Leucyl-OBn · pTsOH (100 mg) was dissolved in $CHCl_3$ (2 mL). Et_3N (51 mg, 75 μL) was added and the solution cooled to 0 °C in an ice

bath. Carbonyldiimidazole (41 mg) was added and the solution stirred at 0 °C for one hour. The bath was removed and the solution was stirred an additional one hour at room temperature. Homopiperidine (44 mg, 50 µL) was added and the solution stirred overnight at room temperature. The solution was washed with saturated $NaHCO_3$ solution, 1 N H_3PO_4 and brine, dried with $MgSO_4$, and evaporated under reduced pressure to give a white solid which was purified by flash chromatography on silica gel, eluting with 25% EtOAc-hexane to give N-(homopiperidin-1-ylcarbonyl)-leucine benzyl ester (77 mg, 88%). The ester was dissolved in EtOH (5 mL), the solution purged of oxygen, 10% Pd/C (0.10 g) added and the mixture stirred under hydrogen for two hours. The solvent was removed *in vacuo* and the residue taken up in EtOAc and filtered through Celite® to remove the catalyst. The solvent was evaporated *in vacuo* to give the carboxylic acid as a white solid (55 mg, 96%).

Example 45E

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-thiazole-4-carboxylic acid

The crude compound resulting from Example 45C (65 mg) was dissolved in THF (2 mL). HOBt (30 mg), the acid resulting from Example 45D (55 mg) and EDCI (42 mg) were added. N-Methylmorpholine (10 µL) was added and the mixture stirred at room temperature for 18 hours. The solvent was evaporated under reduced pressure and the residue taken up in EtOAc. The solution was washed with saturated $NaHCO_3$ solution, 1 N H_3PO_4 and brine, dried with $MgSO_4$, and evaporated *in vacuo* to give an orange oil which was purified by flash chromatography on silica gel eluting with 50% EtOAc-hexane.

The product was dissolved in THF (2 mL), a solution of LiOH (50 mg) in H_2O (1 mL) was added and the mixture warmed at 80 °C for 10 hours. The solvents were evaporated under reduced pressure and the residue purified by preparative HPLC (Vydac µC18) eluting with a 10-70% gradient of CH_3CN in 0.1% TFA. The desired fractions were

lyophilized to give the product as a white solid. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.80 (d, 3H, J=8Hz), 0.82 (d, 3H, J=8Hz), 1.25-1.45 (m, 3H), 1.51 (m, 4H), 1.68 (m, 5H), 2.68 (s, 3H), 3.2-3.45 (m, 6H), 4.29 (dd, 1H, J=6Hz,8Hz), 5.50 (dd, 1H, J=6Hz,8Hz), 6.97 (dt, 1H, J=1Hz,7Hz), 7.04 (s, 1H), 7.08 (dt, 1H, J=1Hz,7Hz), 7.31 (d, 1H, J=8Hz), 7.52 (d, 1H, J=8Hz). MS (DCI/NH_3) m/e 540 $(M+H)^+$, 557 $(M+NH_4)^+$. Anal calcd for $C_{28}H_{37}N_5SO_4 \cdot 1.0$ TFA: C, 55.12; H, 5.86; N, 10.71. Found: C, 55.02; H, 6.06 N, 10.95.

Example 46

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-ethyl-thiazole-4-carboxylic acid

The title compound was prepared according to the procedures described in Example 45, substituting propionyl chloride for acetyl chloride in Example 45A. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.82 (d, 3H, J=7Hz), 0.83 (d, 3H, J=7Hz), 1.24 (t, 3H, J=8Hz), 1.4 (m, 2H), 1.52 (m, 5H), 1.67 (m, 4H), 3.18 (q, 2H, J=8Hz), 3.2-3.5 (m, 6H), 4.30 (dd, 1H, J=6Hz,10Hz), 5.49 (dd, 1H, J=6Hz,8Hz), 6.94 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.04 (s, 1H), 7.07 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.32 (d, 1H, J=8Hz), 7.47 (dd, 1H, J=1Hz,8Hz). MS (DCI/NH_3) m/e 554 $(M+H)^+$, 551 $(M+NH_4)^+$. Anal calcd for $C_{29}H_{39}N_5O_4S \cdot 0.6$ TFA: C, 58.31; H, 6.42; N, 11.26. Found: C, 58.27; H, 6.36; N, 11.26.

Example 47

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-propyl-thiazole-4-carboxylic acid

The title compound was prepared according to the procedures of Example 45, substituting butyryl chloride for acetyl chloride in Example 45A. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.82 (d, 3H, J=7Hz), 0.83 (d, 3H, J=7Hz), 0.93 (t, 3H, J=8Hz), 1.4 (m, 2H), 1.52 (m, 5H), 1.67 (m, 6H), 3.14 (t, 2H, J=8Hz), 3.2-3.5 (m, 6H), 4.30 (dd, 1H, J=6Hz,10Hz), 5.50 (dd, 1H, J=6Hz,8Hz), 6.95 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.04 (s, 1H), 7.06 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.31 (d, 1H, J=8Hz), 7.46 (dd, 1H, J=1Hz,8Hz). MS

(DCI/NH_3) m/e 568 $(M+H)^+$. Anal calcd for $C_{30}H_{41}N_5O_4S \cdot 0.4$ TFA: C, 60.32; H, 6.80; N, 11.42. Found: C, 60.15; H, 6.75; N, 11.33.

Example 48

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-trifluoromethyl-thiazole-4-carboxylic acid

The title compound was prepared according to the procedures of Example 45, substituting trifluoroacetyl chloride for acetyl chloride in Example 45A. ^1H NMR (CD_3OD, 300 MHz) δ 0.78 (d, 3H, J=7Hz), 0.80 (d, 3H, J=7Hz), 1.2-1.4 (m, 2H), 1.52 (m, 5H), 1.68 (m, 4H), 3.3-3.6 (m, 6H), 4.27 (dd, 1H, J=6Hz,10Hz), 5.55 (dd, 1H, J=5Hz,8Hz), 6.97 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.08 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.10 (s, 1H), 7.33 (d, 1H, J=8Hz), 7.48 (dd, 1H, J=1Hz,8Hz). MS (DCI/NH_3) m/e 594 $(M+H)^+$. Anal calcd for $C_{29}H_{34}F_3N_5O_4S \cdot 0.6$ TFA: C, 52.97; H, 5.27; N, 10.58. Found: C, 52.70; H, 5.22; N, 10.50.

Example 49

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-isopropyl-thiazole-4-carboxylic acid

The title compound was prepared according to the procedures of Example 45, substituting isovaleryl chloride for acetyl chloride in Example 45A. ^1H NMR (CD_3OD, 300 MHz) δ 0.83 (d, 3H, J=7Hz), 0.84 (d, 3H, J=7Hz), 1.24 (d, 3H, J=8Hz), 1.25 (d, 3H, J=8Hz), 1.3-1.4 (m, 2H), 1.53 (m, 5H), 1.68 (m, 4H), 2.94 (m, 2H), 3.3-3.5 (m, 6H), 4.09 (septet, 1H, J=7Hz), 4.30 (dd, 1H, J=6Hz,10Hz), 5.49 (dd, 1H, J=6Hz,8Hz), 6.94 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.07 (s, 1H), 7.08 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.30 (d, 1H, J=8Hz), 7.40 (dd, 1H, J=1Hz,8Hz). MS (DCI/NH_3) m/e 568 $(M+H)^+$. Anal calcd for $C_{30}H_{41}N_5O_4S \cdot 1.2$ TFA: C, 55.23; H, 6.04; N, 9.94. Found: C, 55.28; H, 5.13; N, 10.30.

Example 50

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-cyclopropyl-thiazole-4-carboxylic acid

The title compound was prepared according to the procedures of Example 45, substituting cyclopropanecarbonyl chloride for acetyl chloride in Example 45A. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.63 (m, 2H), 0.90 (d, 3H, J=6Hz), 0.91 (d, 3H, J=6Hz), 1.20 (m, 2H), 1.2-1.4 (m, 2H), 1.51 (m, 5H), 1.67 (m, 4H), 2.96 (m, 1H), 3.3-3.6 (m, 6H), 4.28 (dd, 1H, J=6,10Hz), 5.44 (dd, 1H, J=6,8Hz), 6.94 (ddd, 1H, J=1,7,8Hz), 7.05 (s, 1H), 7.08 (ddd, 1H, J=1,7,8Hz), 7.32 (d, 1H, J=8Hz), 7.46 (dd, 1H, J=1,8Hz). MS (DCI/NH_3) m/e 566 $(M+H)^+$. Anal calcd for $C_{30}H_{39}N_5O_4S \cdot 1.2$ TFA: C, 55.39; H, 5.77; N, 9.97. Found: C, 55.43; H, 5.76; N, 10.26.

Example 51

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-phenyl-thiazole-4-carboxylic acid

The title compound was prepared according to the procedures of Example 45, substituting benzoyl chloride for acetyl chloride in Example 45A. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.86 (d, 3H, J=6Hz), 0.87 (d, 3H, J=6Hz), 1.45 (m, 6H), 1.62 (m, 5H), 3.30 (m, 5H), 3.37 (dd, 1H, J=7Hz,15Hz), 3.48 (dd, 1H, J=7Hz,15Hz), 4.32 (brd q, 1H, J=8Hz), 4.70 (brd d, 1H, J=8Hz), 5.60 (brd q, 1H, J= 8Hz), 7.06 (d, 1H, J=2Hz), 7.12 (dt, 1H, J=1Hz,8Hz), 7.20 (dt, 1H, J=1Hz,8Hz), 7.36 (m, 5H), 7.47 (m, 2H), 7.58 (d, 1H, J=8Hz), 8.12 (brd s, 1H). MS (DCI/NH_3) m/e 602 $(M+H)^+$. Anal calcd for $C_{33}H_{39}N_5O_4S \cdot 1.0$ TFA: C, 58.73; H, 5.63; N, 9.78. Found: C, 58.89; H, 5.73; N, 10.16.

Example 52

2-[(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl]-5-benzyl-thiazole-4-carboxylic acid

The title compound was prepared according to the procedures of Example 45, substituting phenylacetyl chloride for acetyl chloride in Example 45A. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.86 (d, 3H, J=6Hz), 0.87 (d, 3H, J=6Hz), 1.48 (m, 6H), 1.63 (m, 5H), 3.24 (m, 4H), 3.34 (m, 3H), 4.32 (brd q, 1H, J=8Hz), 4.52 (s, 1H), 4.57 (brd d, 1H, J=8Hz), 5.50 (brd q, 1H, J= 8Hz), 6.93 (d, 1H, J=2Hz), 7.07 (dt, 1H, J=1Hz,8Hz), 7.18 (m, 2H), 7.26 (m, 5H), 7.34 (dd, 1H, J=7Hz,8Hz), 7.50 (d, 1H, J=8Hz), 8.03 (brd s, 1H). MS (FAB+NBA) m/e 616 $(M+H)^+$, 638 $(M+Na)^+$, 678 $(M+Cu)^+$. HRMS Calcd for $C_{34}H_{42}N_5O_4S$: 616.2958. Found: 616.2943

Example 53

2-[2R-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-3-(indol-3-yl)propyl]-5-methyl-thiazole-4-carboxylic acid

Example 53A

Cbz-α-homo-D-Tryptophanyl-OH

A solution of Cbz-D-Tryptophanyl-OH (2.69 g, 8.1 mmol) in 50 mL of THF was cooled to -20 °C and 0.9 mL (8.1 mmol) of N-methylmorpholine was added, followed by 1.05 mL (8.1 mmol) of isobutyl chloroformate. The resultant slurry was stirred at -20 °C for 40 minutes, and then was filtered through a pad of Celite® to remove the precipitate, washing the pad with ice-cold THF.

An ethereal solution of diazomethane (250 mL of ~0.3 N solution) was cooled to -20 °C in a 500 mL clearseal round-bottom flask. The above mixed-anhydride solution was added dropwise over 15 minutes. After 15 minutes of additional stirring, the bath was removed and the solution allowed to warm to ambient temperature over 150 minutes. The solvents were removed *in vacuo*; the residue was taken up in EtOAc and washed sequentially with water and brine. The organic phase was dried over Na_2SO_4 and stripped *in vacuo*. The crude product was

dissolved in 100 mL of methanol, and a solution of 1.0 g of silver benzoate in 10 mL of triethylamine (filtered through a short pad of Celite) was added over a 5 minute period. After stirring for 60 minutes the solution had turned dark brown. The solvents were removed *in vacuo*; the residue was stirred with 120 mL of a 1:1 water-ethyl acetate mixture for 10 minutes, then filtered through a pad of Celite. The organic layer was washed with brine, dried over Na_2SO_4 and stripped *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with a gradient of 3:1 going to 1:1 hexanes-ethyl acetate to elute the product (2.63 g, 89% yield) as a colorless oil.

A portion of the above material (1.10 g, 3.0 mmol) was dissolved in 15 mL of THF; a solution of 0.15 g of LiOH in 5 mL of water was added. The resultant mixture was stirred at ambient temperature for 3 hours, and then heated to 40 °C for 2 hours. The organic solvent was removed *in vacuo*; the solution was neutralized with 1 N H_3PO_4, then extracted with EtOAc to give the crude acid, which was used without further purification.

Example 53B

2-{2R-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-3-(indol-3-yl)propyl}-5-methyl-thiazole-4-carboxylic acid

The title compound was prepared using the procedures described in Example 45, substituting the compound resulting from Example 53A for Cbz-D-tryptophan in Example 45A. ^1H NMR (CD_3OD, 300 MHz) δ 0.82 (d, 3H, J=6Hz), 0.85 (d, 3H, J=6Hz), 1.15-1.3 (m, 2H), 1.53 (m, 4H), 1.68 (m, 5H), 2.69 (s, 3H), 3.05 (m, 4H), 3.2-3.5 (m, 4H), 4.24 (dd, 1H, J=5Hz,10Hz), 4.55 (m, 1H), 7.00 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.09 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.10 (s, 1H), 7.33 (dd, 1H, J=1Hz,8Hz), 7.57 (dd, 1H, J=1Hz,8Hz). MS (FAB+NBA) m/e 554 $(M+H)^+$, 576 $(M+Na)^+$. Anal calcd for $C_{29}H_{39}N_5O_4S \cdot 1.2$ TFA: C, 54.62; H, 5.87; N, 10.14. Found: C, 54.54; H, 5.88; N, 10.09.

Example 54

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-thiazole-4-carboxylic acid

Example 54A

Boc-D-(N_i-methyl)-Tryptophanyl-$CSNH_2$

A solution of 0.955 g (3.0 mmol) of Boc-D-Trp(Me)-OH, prepared according to the method of Cook *et al.*, Chem. Pharm. Bull. 13(1) 88 (1965), in 25 mL of THF was cooled to -20 °C. N-Methylmorpholine (0.33 mL, 1.0 eq) was added, followed by 0.39 mL (1.0 eq) of isobutyl chloroformate. The resultant slurry was stirred for 30 minutes, and then a solution of 0.2 mL of concentrated ammonia in 3 mL of THF was added. The mixture was warmed slowly to 0 °C over 1 hour. The solvents were removed *in vacuo*, the residue was taken up in ethyl acetate, washed sequentially with water, saturated sodium bicarbonate solution, 1 N H_3PO_4 and brine, dried, and concentrated *in vacuo* to afford 0.95 g (100% yield) of the carboxyamide a white foam.

To a solution of 500 mg (1.57 mmol) of the above compound in 10 mL of THF was added 770 mg (1.90 mmol, 1.2 eq) of Lawesson's reagent. The solution was stirred at ambient temperature for 65 hours. The solvents were removed *in vacuo*, and the residue was taken up in EtOAc and washed sequentially with 1:1 saturated sodium bicarbonate solution/water and brine. The organic phase was dried over Na_2SO_4 and stripped *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with 2:1 hexanes-ethyl acetate to afford the product (442 mg, 86% yield) as a light yellowish foam.

Example 54B

2-(Boc-Amino)-2-(1-methyl-indol-3-yl)ethyl)-thiazole-4-carboxylic acid ethyl ester

The thioamide resulting from Example 54A (100 mg, 0.3 mmol) was combined with 72 mg (0.33 mmol) of ethyl bromopyruvate and 100 mg of propylene oxide in 1 mL of THF in a Carius tube. The solution was heated at 80 °C for 4 hours and then the solvents were removed *in vacuo*. The crude product was taken up in 1 mL of pyridine, and 10 drops of trifluoroacetic anhydride were added slowly. The resultant dark solution was stirred overnight at ambient temperature. The solvents were removed *in vacuo*. The residue was taken up in EtOAc and washed sequentially with 1:1 saturated sodium bicarbonate/water, 1 N H_3PO_4, and brine. The organic phase was dried over Na_2SO_4 and stripped *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with 1:1 hexanes-ethyl acetate to afford the product (125 mg, 99% yield) as a colorless oil.

Example 54C

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-thiazole-4-carboxylic acid

The compound resulting from Example 54B (50 mg) was dissolved in 3 mL of trifluoroacetic acid and stirred at ambient temperature for 45 minutes. The solvents were removed *in vacuo*, and the residue was taken up in saturated sodium bicarbonate solution and extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 and stripped *in vacuo* to give a crude product which was used without further purification. This material was reacted according to the procedures of Example 45E to provide the title compound. ^1H NMR (CD_3OD, 300 MHz) δ 0.80 (d, 6H, J=7Hz), 1.38 (m, 2H), 1.52 (m, 5H), 1.67 (m, 4H), 3.3-3.5 (m, 5H), 3.53 (dt, 1H, J=1Hz,7Hz), 3.74 (s, 3H), 4.50 (dd, 1H, J=6Hz,10Hz), 5.56 (dd, 1H, J=6Hz,9Hz), 6.96 (s, 1H), 7.03 (ddd, 1H, J=1Hz;7Hz,8Hz), 7.14 (dt, 1H, J=1Hz,8Hz), 7.29 (d, 1H, J=8Hz), 7.52 (dd, 1H, J=1Hz,8Hz), 8.24 (s, 1H).

MS (DCI/NH_3) m/e 540 $(M+H)^+$, 557 $(M+H+NH_3)^+$. Anal calcd for $C_{28}H_{38}N_6O_4 \cdot 0.8$ TFA: C, 56.35; H, 6.04; N, 11.10. Found: C, 56.32; H, 6.19; N, 11.40.

Example 55

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-4-trifluoromethyl-thiazole-5-carboxylic acid

The title compound was prepared following the procedures described in Example 54, substituting ethyl 2-chloro trifluoroacetoacetate for ethyl bromopyruvate in Example 54B. ^1H NMR (CD_3OD, 300 MHz) δ 0.78 (d, 6H, J=7Hz), 1.3-1.4 (m, 2H), 1.54 (m, 5H), 1.67 (m, 4H), 3.3-3.5 (m, 5H), 3.55 (d, 1H, J=5Hz), 3.77 (s, 3H), 4.28 (dd, 1H, J=6Hz,9Hz), 5.53 (dd, 1H, J=5Hz,9Hz), 7.02 (dt, 1H, J=1Hz,8Hz), 7.04 (s, 1H), 7.16 (dt, 1H, J=1Hz,8Hz), 7.32 (d, 1H, J=8Hz), 7.47 (d, 1H, J=8Hz). MS (FAB+NBA) m/e 608 $(M+H)^+$. Anal calcd for $C_{29}H_{36}F_3N_5O_4S \cdot 0.4$ TFA: C, 54.79; H, 5.62; N, 10.72. Found: C, 54.79; H, 5.61; N, 10.87.

Example 56

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-thiazole-5-carboxylic acid

The title compound was prepared following the procedures described in Example 54, substituting ethyl 2-chloro-3-oxopropionate for ethyl bromopyruvate in Example 54B. ^1H NMR (CD_3OD, 300 MHz) δ 0.78 (d, 6H, J=7Hz), 1.3-1.4 (m, 2H), 1.52 (m, 5H), 1.67 (m, 4H), 3.3-3.6 (m, 6H), 3.74 (s, 3H), 4.30 (dd, 1H, J=6Hz,9Hz), 5.44 (dd, 1H, J=5Hz,9Hz), 6.97 (s, 1H), 7.02 (dt, 1H, J=1Hz,8Hz), 7.15 (dt, 1H, J=1Hz,8Hz), 7.31 (d, 1H, J=8Hz), 7.48 (d, 1H, J=8Hz), 8.29 (s, 1H). MS (FAB+NBA) m/e 540 $(M+H)^+$. Anal calcd for $C_{28}H_{37}N_5O_4S \cdot 0.6$ TFA: C, 57.68; H, 6.23; N, 11.52. Found: C, 57.38; H, 6.13; N, 11.46.

Example 57

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

Example 57A

Cbz-D-Tryptophanyl-(2-acetylGlycine) ethyl ester

N-(Diphenylmethylene)glycine ethyl ester (30.0 g) was dissolved in THF (125 mL) and the solution cooled to -78 °C. Lithium hexamethyldisilazide (100 mL, 1 N solution in THF) was added slowly over 10 minutes, and the resulting yellow slurry was stirred at -78 °C for 45 minutes. The slurry was then transferred via cannula to a solution of acetyl chloride (8.4 mL) in THF (50 mL) at -78 °C . Additional THF (250 mL) was added to the anion solution to facilitate transfer to the acetyl chloride solution. Complete transfer of the anion took about 2.5 hours. After the addition was complete, the reaction was allowed to warm to room temperature and stirring was continued for four hours. The reaction was then quenched with 2 N HCl (115 mL). The THF was evaporated and the resulting aqueous solution was washed with EtOAc (2 x 100 mL). The organic phases were discarded and the aqueous phase was concentrated *in vacuo*. The resulting slurry was treated with EtOH (150 mL) and the insolubles filtered off. The filtrate was evaporated to give 2-acetylglycine ethyl ester hydrochloride as a yellow solid which was used without further purification.

Cbz-D-Tryptophan (40.6 g) was dissolved in THF (100 mL) and the solution cooled to -20 °C. N-Methylmorpholine (13 mL) was added followed by the dropwise addition of isobutylchloroformate (15.6 mL). After the addition was complete, the reaction was stirred for 30 minutes at -20 °C at which time the bath was removed. The 2-acetylglycine ester from above was dissolved in DMF (50 mL) and added to the mixed anhydride. N-Methylmorpholine (13 mL) was then added via syringe pump over a one hour period. After the addition was complete, the reaction was allowed to stir at room temperature for one hour. Water (200 mL) was added and the layers separated. The organic layer was

washed with saturated $NaHCO_3$ solution, 1 N H_3PO_4 and brine, dried with $MgSO_4$, and evaporated under reduced pressure to give an orange oil which was purified by flash chromatography on silica gel eluting with 15% EtOAc-hexane. The title compound was isolated as an orange oil (30.7 g, 59% yield for the two steps). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.26 (dt, 3H, J=1Hz,7Hz), 2.24 (s, 1.5H), 2.30 (s, 1.5H), 3.20 (m, 1H), 3.35 (m, 1H), 4.22 (dq, 2H, J=1Hz,7Hz), 4.50 (m, 1H), 5.06 (dd, 1H, J=7Hz,8Hz), 5.12 (s, 2H), 5.45 (m, 1H), 6.82 (m, 1H), 7.23 (m, 9H), 7.65 (m, 1H), 8.10 (s, 1H). MS (DCI/NH_3) m/e 466 $(M+H)^+$, 483 $(M+NH_4)^+$.

Example 57B

2-[(1R)-(Benzyloxycarbonylamino)-2-(indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid ethyl ester

The compound resulting from Example 57A (4.44 g) was dissolved in acetonitrile (15 mL). Pyridine (25 mL), carbon tetrachloride (2 mL), DBU (2.90 g) and triphenylphosphine (2.75 g) were added, and the mixture was stirred for 16 hours at room temperature. The solvents were evaporated under reduced pressure and the residue dissolved in EtOAc. The solution was washed with saturated $NaHCO_3$ solution, 1 N H_3PO_4, and brine, dried with $MgSO_4$ and evaporated to give an off-white semi-solid which was purified by flash chromatography on silica gel eluting with 15% EtOAc-hexane to give the title compound. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.37 (t, 3H, J=7Hz), 2.50 (s, 3H), 3.40 (d, 2H, J=8Hz), 4.37 (q, 2H, J=7Hz), 5.08 (s, 2H), 5.28 (m, 1H), 5.48 (m, 1H), 6.89 (s, 1H), 7.05 (t, 1H, J=8Hz), 7.16 (t, 1H, J=8), 7.35 (m, 7H), 8.06 (s, 1H). MS (DCI/NH_3) m/e 448 $(M+H)^+$, 465 $(M+NH_4)^+$.

Example 57C

2-[(1R)-Amino-2-(indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid ethyl ester

The compound resulting from Example 57B (90 mg) was dissolved in EtOH (5 mL) and 10% Pd/C (50 mg) was added. The mixture was purged of oxygen and stirred under a balloon of hydrogen for 5 hours. The solvent was removed *in vacuo* and the residue taken up in EtOAc and filtered through Celite® to remove the catalyst . The solvent was evaporated to give the ethyl ester as a yellow oil.

Example 57D

N-(Homopiperidin-1-ylcarbonyl)-Leucyl-OH

Leucyl-OBn · pTsOH (100 mg) was dissolved in $CHCl_3$ (2 mL). Et_3N (51 mg, 75 µL) was added and the solution cooled to 0 °C in an ice bath. Carbonyldiimidazole (41 mg) was added and the solution stirred at 0 °C for one hour. The bath was removed and the solution was stirred an additional one hour at room temperature. Homopiperidine (44 mg, 50 µL) was added and the solution stirred overnight at room temperature. The solution was washed with saturated $NaHCO_3$ solution, 1 N H_3PO_4 and brine, dried with $MgSO_4$, and evaporated under reduced pressure to give a white solid which was purified by flash chromatography on silica gel, eluting with 25% EtOAc-hexane to give N-(homopiperidin-1-ylcarbonyl)-leucine benzyl ester (77 mg, 88%). The ester was dissolved in EtOH (5 mL), the solution purged of oxygen, 10% Pd/C (0.10 g) added and the mixture stirred under hydrogen for two hours. The solvent was removed *in vacuo* and the residue taken up in EtOAc and filtered through Celite® to remove the catalyst. The solvent was evaporated *in vacuo* to give the carboxylic acid as a white solid (55 mg, 96%).

Example 57E

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The compound resulting from Example 57C (68 mg) was dissolved in THF (2 mL). HOBt (30 mg), the acid resulting from Example 57D (55 mg) and EDCI (42 mg) were added. N-Methylmorpholine (10 µL) was added and the mixture stirred at room temperature for 18 hours. The solvent was evaporated under reduced pressure and the residue taken up in EtOAc. The solution was washed with saturated $NaHCO_3$ solution, 1 N H_3PO_4 and brine, dried with $MgSO_4$, and evaporated *in vacuo* to give an orange oil which was purified by flash chromatography on silica gel eluting with 50% EtOAc-hexane.

To this compound dissolved in THF (2 mL) was added a solution of LiOH (50 mg) in H_2O (1 mL) and the mixture stirred at room temperature for 15 hours. The solvents were evaporated under reduced pressure and the residue purified by preparative HPLC (Vydac µC18) eluting with a 10-70% gradient of CH_3CN in 0.1% TFA. The desired fractions were lyophilized to give the product as a white solid. ^1H NMR (CD_3OD, 300 MHz) δ 0.87 (d, 3H, J=7Hz), 0.88 (d, 3H, J=7Hz), 1.43 (m, 2H), 1.52 (m, 5H), 1.67 (m, 4H), 2.55 (s, 3H), 3.25-3.5 (m, 6H), 4.34 (dd, 1H, J=6Hz,9Hz), 5.40 (t, 1H, J=7Hz), 6.95 (ddd, 1H, J=1Hz,7Hz,8Hz), 6.99 (s, 1H), 7.07 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.31 (td, 1H, J=1Hz,8Hz), 7.37 (d, 1H, J=8Hz). MS (DCI/NH_3) m/e 524 $(M+H)^+$, 541 $(M+NH_4)^+$. Anal calcd for $C_{28}H_{37}N_5O_5 \cdot 0.4$ TFA: C, 60.77; H, 6.62; N, 12.34. Found: C, 60.72; H, 6.55; N, 12.39.

Example 58

2-{(1R)-1-[(Cyclohexylaminocarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared following the procedures described in Example 57, substituting cyclohexylamine for homopiperidine in Example 57D. ^1H NMR (CD_3OD, 300 MHz) δ 0.78 (d, 3H, 7Hz), 0.79 (d, 3H, 7Hz), 1.0-1.80 (m, 13H), 2.58 (s, 3H), 3.42 (m,

3H), 4.20 (t, 1H, J=7Hz), 5.42 (d, 1H, J=7Hz), 6.96 (t, 1H, J=7Hz), 7.03 (s, 1H), 7.06 (t, 1H, J=7Hz), 7.31 (d, 1H, J=7Hz), 7.44 (d, 1H, J=7Hz). MS (DCI/NH_3) m/e 524 $(M+H)^+$. Anal calcd for $C_{28}H_{37}N_5O_5 \cdot 0.8$ TFA: C, 57.82; H, 6.20; N, 11.39. Found: C, 57.69; H, 6.42; N, 11.40.

Example 59

2-{(1R)-1-[(4-Methoxymethoxypiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared following the procedures described in Example 57, substituting 4-methoxymethoxypiperidine for homopiperidine in Example 57D. ^1H NMR (CD_3OD) δ 0.83 (d, 3H, J=7Hz), 0.85 (d, 3H, J=7Hz), 1.3-1.55 (m, 5H), 2.53 (s, 3H), 3.12 (m, 2H), 3.35 (s, 3H), 3.36 (m, 2H), 3.70 (m, 3H), 4.30 (dd, 1H, J=6,7Hz), 4.68 (s, 2H), 5.39 (t, 1H, J=8Hz), 6.95 (t, 1H, J=7Hz), 7.01 (s, 1H), 7.07 (t, 1H, J=7Hz), 7.30 (d, 1H, J=7Hz), 7.37 (d, 1H, J=7Hz). MS (DCI/NH_3) m/e 570 $(M+H)^+$, 571 $(M+NH_4)^+$. Anal calcd for $C_{29}H_{39}N_5O_7 \cdot 0.6$ TFA: C, 56.85; H, 6.26; N, 10.98. Found: C, 56.96; H, 5.83; N, 10.98.

Example 60

2-{(1R)-1-[N-(Homopiperidin-1-ylsulfonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

Example 60A

N-(Homopiperidin-1-ylsulfonyl)-Leucine

Homopiperidine (6 mL) was dissolved in diethyl ether (250 mL) and cooled to 0 °C in an ice bath. HCl gas was bubbled through the solution. The resulting white solid was collected by filtration and dried *in vacuo*. The solid was taken up in sulfuryl chloride (20 mL) and the mixture heated at reflux. The reaction became very thick and additional sulfuryl chloride (10 mL) was added and reflux continued for 16 hours. The remaining sulfuryl chloride was evaporated and the residue distilled (90-100 °C, 0.1 mm) to give homopiperidinesulfonyl chloride as a colorless oil (9.06 g, 86%). The sulfonyl choride (0.97 g) was dissolved

in DMF (10 mL). Leu-OBn · pTsOH (2.03 g), Hünig's base (1.75 mL), and then DMAP (0.2 g) were added and the mixture stirred at room temperature for 16 hours. The solution was diluted with ethyl acetate, washed with water, 2 N HCl, saturated $NaHCO_3$ solution, and brine, dried, and evaporated. Purification by flash chromatography (10% EtOAc-hexane) gave N-(homopiperidin-1-ylsulfonyl)-leucine benzyl ester as a white solid (0.88 g, 47%). The benzyl ester (0.85 g) was dissolved in MeOH (20 mL) and 10% Pd/C (0.75 g) was added. The mixture was stirred at room temperature under an H_2 atmosphere for 2.5 hours. The catalyst was filtered off and the solvent evaporated to give the title compound as a colorless oil (0.66 g, 100%).

Example 60B

2-{(1R)-1-[N-(Homopiperidin-1-ylsulfonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared following the procedures described in Example 57E, substituting the compound resulting from Example 60A for N-(homopiperidin-1-ylcarbonyl)-Leucyl-OH. ^1H NMR (CD_3OD, 300 MHz) δ 0.83 (d, 3H, J=6Hz), 0.90 (d, 3H, J=6Hz), 1.4-1.8 (m, 11H), 2.49 (s, 3H), 2.57 (s, 3H), 2.88 (dd, 1H, J=9Hz,15Hz), 3.2-3.5 (m, 5H), 4.20 (dd, 1H, J=6Hz,11Hz), 5.34 (dd, 1H, J=7Hz,8Hz), 6.95 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.07 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.10 (s, 1H), 7.31 (td, 1H, J=1Hz,8Hz), 7.40 (td, 1H, J=1Hz,8Hz). MS (FAB+NBA) m/e 538 $(M+H)^+$, 560 $(M+Na)^+$. Anal calcd for $C_{29}H_{39}N_5O_5 \cdot 1.0$ TFA: C, 57.14; H, 6.19; N, 10.75. Found: C, 56.76; H, 6.23; N, 10.71.

Example 61

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-phenyl-oxazole-4-carboxylic acid

The title compound was prepared following the procedures described in Example 57, substituting benzoyl chloride for acetyl chloride in Example 57A. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.84 (d, 3H, J=6Hz), 0.85 (d, 3H, J=6Hz), 1.47 (m, 7H), 1.62 (m, 4H), 3.2-3.4 (m, 5H),

3.47 (d, 2H, J=7Hz), 4.40 (brd q, 1H, J=8Hz), 4.87 (brd d, 1H, J=8Hz), 5.60 (q, 1H, J= 8Hz), 7.02 (d, 1H, J=1Hz), 7.07 (t, 1H, J=8Hz), 7.16 (t, 1H, J=8Hz), 7.33 (d, 1H, J=8Hz), 7.40 (m, 4H), 7.53 (d, 1H, J=8Hz), 7.94 (m, 2H), 8.13 (brd s, 1H). MS (FAB+NBA) m/e 586 $(M+H)^+$. HRMS Calcd for $C_{33}H_{40}N_5O_5$: 586.3029. Found: 586.3033.

Example 62

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-benzyl-oxazole-4-carboxylic acid

The title compound was prepared following the procedures described in Example 57, substituting phenylacetyl chloride for acetyl chloride in Example 57A. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.84 (d, 3H, J=6Hz), 0.85 (d, 3H, J=6Hz), 1.50 (m, 7H), 1.66 (m, 4H), 3.2-3.5 (m, 6H), 4.18 (d, 1H, J=15Hz), 4.32 (d, 1H, J=15Hz), 4.45 (brd q, 1H, J=8Hz), 4.94 (brd d, 1H, J=8Hz), 5.46 (q, 1H, J= 8Hz), 6.70 (d, 1H, J=2Hz), 7.03 (dt, 1H, J=1Hz,8Hz), 7.14 (dt, 1H, J=1Hz,8Hz), 7.19 (m, 2H), 7.26 (m, 5H), 7.37 (brd s, 1H), 7.46 (d, 1H, J=8Hz), 7.88 (brd s, 1H). MS (FAB+NBA) m/e 600 $(M+H)^+$, 622 $(M+Na)^+$. Anal calcd for $C_{34}H_{41}N_5O_5 \cdot 0.6$ TFA: C, 63.28; H, 6.28; N, 10.48. Found: C, 63.50; H, 6.16; N, 10.51.

Example 63

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-ethyl-oxazole-4-carboxylic acid

The title compound was prepared following the procedures described in Example 57, substituting propionyl chloride for acetyl chloride in Example 57A. ^1H NMR (CD_3OD, 300 MHz) δ 0.87 (d, 3H, J=7Hz), 0.88 (d, 3H, J=7Hz), 1.14 (t, 3H, J=8Hz), 1.4 (m, 2H), 1.54 (m, 5H), 1.68 (m, 4H), 2.94 (dq, 2H, J=2Hz,8Hz), 3.2-3.5 (m, 6H), 4.37 (dd, 1H, J=6Hz,10Hz), 5.39 (t, 1H, J=6Hz), 6.94 (ddd, 1H, J=1Hz,7Hz,8Hz), 6.98 (s, 1H), 7.07 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.33 (td, 1H, J=1Hz,8Hz), 7.34 (dd, 1H, J=1Hz,8Hz). MS (FAB/NBA) m/e 538 $(M+H)^+$. Anal calcd

for $C_{29}H_{39}N_5O_5 \cdot 0.7$ TFA: C, 59.14, H, 6.48, N, 11.34. Found: C, 58.94, H, 6.47, N, 11.92.

Example 64

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-propyl-oxazole-4-carboxylic acid

The title compound was prepared following the procedures described in Example 57, substituting butyryl chloride for acetyl chloride in Example 57A. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.85 (d, 3H, J=7Hz), 0.86 (d, 3H, J=7Hz), 0.90 (t, 3H, J=8Hz), 1.4-1.5 (m, 2H), 1.53 (m, 5H), 1.60 (m, 2H), 1.68 (m, 4H), 2.94 (dt, 2H, J=2Hz,8Hz), 3.3-3.6 (m, 6H), 4.36 (dd, 1H, J=6Hz,10Hz), 5.38 (t, 1H, J=6Hz), 6.95 (ddd, 1H, J=1Hz,7Hz,8Hz), 6.97 (s, 1H), 7.07 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.30 (d, 1H, J=8Hz), 7.35 (d, 1H, J=8Hz). MS (DCI/NH_3) m/e 552 $(M+H)^+$, 569 $(M+NH_4)^+$. Anal calcd for $C_{30}H_{41}N_5O_5 \cdot 0.3$ TFA: C, 62.73; H, 7.11; N, 11.95. Found: C, 62.43; H, 6.95; N, 11.79.

Example 65

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-cyclopropyl-oxazole-4-carboxylic acid

The title compound was prepared following the procedures described in Example 57, substituting cyclopropylcarbonyl chloride for acetyl chloride in Example 57A. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.84 (d, 3H, J=6Hz), 0.86 (d, 3H, J=6Hz), 0.87 (m, 2H), 1.04 (dd, 2H, J=3Hz,9Hz), 1.4 (m, 2H), 1.53 (m, 5H), 1.68 (m, 4H), 2.65 (m, 1H), 3.3-3.6 (m, 6H), 4.34 (dd, 1H, J=6Hz,10Hz), 5.34 (t, 1H, J=7Hz), 6.95 (ddd, 1H, J=1Hz,7Hz,8Hz), 6.97 (s, 1H), 7.07 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.32 (d, 1H, J=8Hz), 7.34 (dd, 1H, J=1Hz,8Hz). MS (DCI/NH_3) m/e 550 $(M+H)^+$, 567 $(M+NH_4)^+$. Anal calcd for $C_{30}H_{39}N_5O_5 \cdot 0.8$ TFA: C, 59.22; H, 6.26; N, 10.93. Found: C, 58.92, H, 5.96, N, 10.83.

Example 66

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-isopropyl-oxazole-4-carboxylic acid

The title compound was prepared following the procedures described in Example 57, substituting isovaleryl chloride for acetyl chloride in Example 57A. ^{1}H-NMR (CD_3OD, 300 MHz) δ 0.87 (d, 3H, J=6Hz), 0.89 (d, 3H, J=6Hz), 1.15 (d, 3H, J=7Hz), 1.18 (d, 3H, J=7Hz), 1.4-1.5 (m, 2H), 1.52 (m, 5H), 1.68 (m, 4H), 3.3-3.5 (m, 6H), 3.69 (m, 1H), 4.38 (dd, 1H, J=6Hz,10Hz), 5.37 (t, 1H, J=6Hz), 6.93 (ddd, 1H, J=1Hz,7Hz,8Hz), 6.97 (s, 1H), 7.06 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.30 (d, 2H, J=9Hz). MS (DCI/NH_3) m/e 552 $(M+H)^+$, 569 $(M+NH_4)^+$. Anal calcd for $C_{30}H_{41}N_5O_5 \cdot 0.9$ TFA: C, 58.38, H, 6.45, N, 10.70. Found: C, 58.54, H, 6.45, N, 10.75.

Example 67

2-{(1R)-1-[N-(N-Homopiperidin-1-ylcarbonyl-N-methyl-Leucyl)-amino]-2-(indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared following the procedures described in Example 57, substituting (N-methyl)Leu-OBn for Leu-OBn in Example 57D. ^{1}H-NMR (CD_3OD, 300 MHz) δ 0.83 (d, 3H, J=6Hz), 0.90 (d, 3H, J=6Hz), 1.4-1.8 (m, 11H), 2.49 (s, 3H), 2.57 (s, 3H), 2.88 (dd, 1H, J=9Hz,15Hz), 3.2-3.5 (m, 5H), 4.20 (dd, 1H, J=6Hz,11Hz), 5.34 (dd, 1H, J=7Hz,8Hz), 6.95 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.07 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.10 (s, 1H), 7.31 (td, 1H, J=1Hz,8Hz), 7.40 (td, 1H, J=1Hz,8Hz). MS (FAB+NBA) m/e 538 $(M+H)^+$, 560 $(M+Na)^+$. Anal calcd for $C_{29}H_{39}N_5O_5 \cdot 1.0$ TFA: C, 57.14, H, 6.19, N, 10.75. Found: C, 56.76, H, 6.23, N, 10.71.

Example 68

2-[(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid ethyl ester

The compound resulting from Example 57C (68 mg) was dissolved in THF (2 mL). HOBt (30 mg), the acid prepared in Example 57D (55 mg) and EDCI (42 mg) were added. N-Methylmorpholine (10 µL) was added and the mixture stirred at room temperature for 18 hours. The solvent was evaporated under reduced pressure and the residue taken up in EtOAc. The solution was washed with saturated $NaHCO_3$ solution, 1 N H_3PO_4 and brine, dried with $MgSO_4$, and evaporated *in vacuo* to give an orange oil which was purified by flash chromatography on silica gel eluting with 50% EtOAc-hexane. ^1H NMR (CD_3OD, 300 MHz) δ 0.87 (d, 3H, J=7Hz), 0.88 (d, 3H, J=7Hz), 1.34 (t, 3H, J=8Hz), 1.43 (m, 2H), 1.52 (m, 5H), 1.67 (m, 4H), 2.55 (s, 3H), 3.25-3.5 (m, 6H), 4.32 (q, 2H, J=8Hz), 4.35 (dd, 1H, J=5Hz,9Hz), 5.39 (t, 1H, J=8Hz), 6.95 (ddd, 1H, J=1Hz,7Hz,8Hz), 6.98 (s, 1H), 7.07 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.31 (td, 1H, J=1Hz,8Hz), 7.36 (d, 1H, J=8Hz). MS (DCI/NH_3) m/e 552 $(M+H)^+$, 569$(M+NH_4)^+$. Anal calcd for $C_{30}H_{41}N_5O_5 \cdot 0.4$ TFA: C, 61.94; H, 6.99; N, 11.73. Found: C, 62.02; H, 7.08; N, 11.70.

Example 69

2-[(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl]-5-methyl-oxazole-4-(N-hydroxy)carboxamide

The compound resulting from Example 57E was dissolved in 3 mL of THF and cooled to 0 °C. Oxalyl chloride (20 µL) and one drop of DMF were added and the solution stirred for 90 minutes at 0 °C. Hydroxylamine was dissolved in 2 mL of THF and cooled to 0 °C. The acid chloride solution was added, and the mixture was allowed to warm to room temperature and stirred overnight. The solvents were evaporated and the residue purified by preparative HPLC (Vydac µC18) eluting with a 10-70% gradient of CH_3CN in 0.1% TFA. The desired fractions were lyophilized to give the title compound as a white solid. ^1H NMR (CD_3OD, 300 MHz) δ 0.84 (d, 3H, J=7Hz), 0.85 (d, 3H, J=7Hz), 1.4

(m, 2H), 1.52 (m, 5H), 1.67 (m, 4H), 2.53 (s, 3H), 3.25-3.5 (m, 6H), 4.29 (dd, 1H, J=6Hz,10Hz), 5.36 (dd, 1H, J=7Hz,8Hz), 6.97 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.02 (s, 1H), 7.07 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.31 (td, 1H, J=1Hz,8Hz), 7.44 (td, 1H, J=1Hz,8Hz). MS (DCI/NH_3) m/e 539 $(M+H)^+$. Anal calcd for $C_{28}H_{38}N_6O_5 \cdot 0.8$ TFA: C, 56.45; H, 6.21; N, 13.34. Found: C, 56.51; H, 6.09; N, 13.13.

Example 70

2-[(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl]-5-methyl-oxazole-4-(N-methyl)carboxamide

The title compound was prepared by the procedure described in Example 69 but substituting 40% aqueous methylamine for hydroxylamine. ^1H NMR (CD_3OD, 300 MHz) δ 0.85 (d, 3H, J=7Hz), 0.86 (d, 3H, J=7Hz), 1.3-1.5 (m, 2H), 1.52 (m, 5H), 1.67 (m, 4H), 2.52 (s, 3H), 2.85 (s, 3H), 2.93 (m, 1H), 3.3-3.5 (m, 6H), 4.30 (dd, 1H, J=6Hz,10Hz), 5.36 (dd, 1H, J=7Hz,8Hz), 6.97 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.00 (s, 1H), 7.07 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.31 (td, 1H, J=1Hz,8Hz), 7.44(td, 1H, J=1Hz,8Hz). MS (DCI/NH_3) m/e 537 $(M+H)^+$. Anal calcd for $C_{29}H_{40}N_6O_4 \cdot 0.3$ TFA: C, 62.28; H, 7.12; N, 14.72. Found: C, 61.97; H, 7.06; N, 12.71.

Example 71

2-[(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl]-5-methyl-oxazole-4-(N-carboxymethyl)carboxamide

The title compound was prepared by the procedure described in Example 69 substituting glycine ethyl ester for hydroxylamine. The resulting product was dissolved in THF (2 mL), a solution of LiOH (50 mg) in H_2O (1 mL) was added and the mixture was stirred at room temperature for 15 hours. The solvents were evaporated under reduced pressure and the residue purified by preparative HPLC (Vydac μC18) eluting with a 10-70% gradient of CH_3CN in 0.1% TFA. The desired fractions were lyophilized to give the product as a white solid. ^1H NMR (CD_3OD, 300 MHz) δ 0.84 (d, 3H, J=7Hz), 0.85 (d, 3H, J=7Hz), 1.4 (m,

2H), 1.52 (m, 5H), 1.67 (m, 4H), 2.52 (s, 3H), 3.3-3.5 (m, 6H), 4.04 (s, 2H), 4.31 (dd, 1H, J=6Hz,10Hz), 5.39 (dd, 1H, J=7Hz,8Hz), 6.97 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.03 (s, 1H), 7.07 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.30 (td, 1H, J=1Hz,8Hz), 7.45 (td, 1H, J=1Hz,8Hz). MS (DCI/NH_3) m/e 581$(M+H)^+$. Anal calcd for $C_{30}H_{40}N_6O_6 \cdot 0.7$ TFA: C, 57.10; H, 6.21; N, 12.72. Found: C, 57.27; H, 6.20; N, 12.71.

Example 72

2-[(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl]-5-methyl-oxazole-4-acetic acid

Example 72A

2-[(1R)-1-(Cbz-Amino)-2-(indol-3-yl)ethyl]-5-methyl-oxazole-4-acetic acid

A solution of the compound resulting from Example 57B (200 mg, 0.46 mmol) in 4 mL of THF was combined with 40 mg of LiOH in 1 mL of water. The mixture was stirred at ambient temperature for 65 hours and then heated at 45 °C for 3 hours. The organic solvent was removed *in vacuo*; the aqueous solution was neutralized with 1N H_3PO_4 and then extracted with EtOAc. The combined organic extracts were concentrated *in vacuo* to give the crude acid, which was used without further purification.

To the above crude acid dissolved in 5 mL of THF and cooled to -20 °C was added 100 µL of N-methylmorpholine, followed by 60 µL of isobutyl chloroformate. The resultant slurry was stirred at -20 °C for 45 minutes. An ethereal solution of diazomethane (10 mL of ~0.3 N) was added dropwise, and the mixture was allowed to warm to ambient temperature over 3.5 hours. The solvents were removed *in vacuo*; the residue was taken up in EtOAc and washed sequentially with water and brine. The organic phase was dried over Na_2SO_4 and stripped *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with 1:1 hexanes-ethyl acetate.

To the diazoketone prepared above dissolved in 10 mL of methanol was added a solution of 150 mg of silver benzoate in 2 mL of triethylamine (filtered through a short pad of Celite) over a 10-minute period. After stirring for 2 hours the solution had turned dark brown. The solvents were removed *in vacuo*; the residue was stirred with 120 mL of a 1:1 water-ethyl acetate mixture for 10 minutes and then filtered through a pad of Celite. The organic layer was washed with brine, dried over Na_2SO_4 and stripped *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with a gradient of 1:1 going to 2:1 ethyl acetate-hexanes to afford the product (13 mg, 6% yield) as a colorless oil.

Example 72B

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-oxazole-4-acetic acid

The title compound was prepared following the procedures described in Example 57C-E, substituting the compound resulting from Example 72A for 2-{(1R)-(Benzyloxycarbonylamino)-2-(indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid ethyl ester in Example 57C. ^1H NMR (CD_3OD, 300 MHz) δ 0.85 (d, 6H, J=6Hz), 0.94 (m, 1H), 1.40 (m, 1H), 1.52 (m, 5H), 1.66 (m, 4H), 2.24 (s, 3H), 3.3-3.5 (m, 6H), 3.45 (s, 2H), 4.33 (dd, 1H, J=6Hz,9Hz), 5.37 (7, 1H, J=7Hz), 6.96 (ddd, 1H, J=1Hz,7Hz,8Hz), 6.97 (s, 1H), 7.07 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.29 (td, 1H, J=1Hz,8Hz), 7.36 (td, 1H, J=1Hz,8Hz). MS (DCI/NH_3) m/e 538 $(M+H)^+$. HRMS Calcd for $C_{29}H_{40}N_5O_5$: 538.3029. Found: 358.3030.

Example 73

2-{2R-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-3-(indol-3-yl)propyl}-5-methyl-oxazole-4-carboxylic acid

Example 73A

Cbz-α-homo-D-Tryptophanyl-OH

A solution of Cbz-D-Tryptophanyl-OH (2.69 g, 8.1 mmol) in 50 mL of THF was cooled to -20 °C and 0.9 mL (8.1 mmol) of N-methylmorpholine was added, followed by 1.05 mL (8.1 mmol) of isobutyl chloroformate. The resultant slurry was stirred at -20 °C for 40 minutes, and then was filtered through a pad of Celite® to remove the precipitate, washing the pad with ice cold THF.

An ethereal solution of diazomethane (250 mL of ~0.3 N solution) was cooled to -20 °C in a 500-mL clearseal round-bottom flask. The above mixed-anhydride solution was added dropwise over 15 minutes. After 15 minutes of additional stirring, the bath was removed and the solution allowed to warm to ambient temperature over 150 minutes. The solvents were removed *in vacuo*; the residue was taken up in EtOAc and washed sequentially with water and brine. The organic phase was dried over Na_2SO_4 and stripped *in vacuo*. The crude product was dissolved in 100 mL of methanol, and a solution of 1.0 g of silver benzoate in 10 mL of triethylamine (filtered through a short pad of Celite) was added over a 5-minute period. After stirring for 60 minutes the solution had turned dark brown. The solvents were removed *in vacuo*; the residue was stirred with 120 mL of a 1:1 water-ethyl acetate mixture for 10 minutes, then filtered through a pad of Celite. The organic layer was washed with brine, dried over Na_2SO_4 and stripped *in vacuo*. The crude product was purified by flash chromatography on silica gel eluting with a gradient of 3:1 going to 1:1 hexanes-ethyl acetate to elute the product (2.63 g, 89% yield) as a colorless oil.

A portion of the above material (1.10 g, 3.0 mmol) was dissolved in 15 mL of THF; a solution of 0.15 g of LiOH in 5 mL of water was added. The resultant mixture was stirred at ambient temperature for 3

hours, and then heated to 40 °C for 2 hours. The organic solvent was removed *in vacuo*; the solution was neutralized with 1 N H_3PO_4, then extracted with EtOAc to give the crude acid, which was used without further purification.

Example 73B

2-{2R-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-3-(indol-3-yl)propyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared following the procedures described in Example 57, substituting the compound resulting from Example 73A for Cbz-D-Tryptophan in Example 57A. ^1H NMR (CD_3OD, 300 MHz) δ 0.83 (d, 3H, J=6Hz), 0.86 (d, 3H, J=6Hz), 1.1-1.2 (m, 2H), 1.53 (m, 4H), 1.68 (m, 5H), 2.52 (s, 3H), 2.88 (dd, 1H, J=9Hz,15Hz), 3.05 (m, 3H), 3.2-3.5 (m, 4H), 4.22 (dd, 1H, J=5Hz,10Hz), 4.62 (m, 1H), 7.00 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.08 (s, 1H), 7.09 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.33 (td, 1H, J=1Hz,8Hz), 7.56 (td, 1H, J=1Hz,8Hz). MS (FAB+NBA) m/e 538 $(M+H)^+$, 560 $(M+Na)^+$. Anal calcd for $C_{29}H_{39}N_5O_5 \cdot 0.9$ TFA: C, 57.78; H, 6.28; N, 10.94. Found: C, 57.50; H, 6.22; N, 10.75.

Example 74

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared following the procedures described in Example 57, substituting Cbz-D-Trp(1-methyl)-OH, prepared according to the method of Cook, *et al.*, Chem. Pharm. Bull. 13 88 (1965), for Cbz-D-Trp-OH in Example 57A. ^1H NMR (CD_3OD, 300 MHz) δ 0.86 (d, 6H, J=7Hz), 1.4 (m, 2H), 1.53 (m, 5H), 1.67 (m, 4H), 2.54 (s, 3H), 3.25-3.5 (m, 6H), 3.73 (s, 3H), 4.33 (dd, 1H, J=6Hz,10Hz), 5.37 (t, 1H, J=7Hz), 6.93 (s, 1H), 6.99 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.04 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.31 (d, 1H, J=8Hz), 7.40 (td, 1H, J=1Hz,8Hz). MS (DCI/NH_3) m/e 538 $(M+H)^+$, 555 $(M+NH_4)^+$. Anal calcd for $C_{29}H_{39}N_5O_5 \cdot 1.0$ TFA: C, 57.14; H, 6.19; N, 10.75. Found: C, 56.96; H, 6.16; N, 10.71.

Example 75

2-{(1R)-1-[(N-Boc-Leucyl)-amino]-2-(indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

Example 75A

2-{(1R)-1-[N-Boc-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid ethyl ester

The compound resulting from Example 57B (1.7 g) was dissolved in EtOH (10 mL). 10% Pd/C (0.5 g) was added and the mixture stirred at room temperature under an atmosphere of hydrogen. After two hours the catalyst was removed by filtration and the solvent evaporated *in vacuo* to give a white solid (1.2 g). The solid was dissolved in THF (10 mL) and added to a solution of Boc-Leu-OH · H_2O (1.0 g) and HOBt (0.5 g) in THF (10 mL). EDCI (0.75 g) was added to the solution, followed by DMF (2 mL). The mixture was stirred for 20 hours at room temperature. The solvent was evaporated *in vacuo* and the residue taken up in EtOAc. The solution was washed with saturated $NaHCO_3$ solution, 1 N H_3PO_4, and brine, dried with $MgSO_4$, and evaporated to give an orange solid that was purified by flash chromatography eluting with 25% EtOAc-hexane to afford (1.85 g, 92%) of the title compound. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.84 (d, 6H, J=8Hz), 1.38 (t, 3H, J=8Hz), 1.39 (s, 9H), 1.43 (m, 3H), 2.50 (s, 3H), 3.40 (d, 2H, J=8Hz), 4.18 (br s, 1H), 4.39 (q, 2H, J=8Hz), 4.80 (m, 1H), 5.51 (q, 1H, J=8Hz), 6.65 (d, 1H, J=10Hz), 6.97 (s, 1H), 7.08 (t, 1H, J=8Hz), 7.17 (t, 1H, J=8Hz), 7.32 (d, 1H, J=8Hz), 7.45 (m, 1H, J=8Hz), 8.05 (s, 1H). MS (DCI/NH_3) m/e 526 $(M+H)^+$, 544 $(M+NH_4)^+$.

Example 75B

2-[(1R)-1-[(N-Boc-Leucyl)-amino]-2-(indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid

To the compound resulting from Example 75A (100 mg) dissolved in THF (2 mL) was added a solution of LiOH (50 mg) in H_2O (1 mL). The mixture was stirred at room temperature for 15 hours. The solvents were evaporated under reduced pressure and the residue purified by preparative HPLC (Vydac μC18) eluting with a 10-70% gradient of CH_3CN in 0.1% TFA. The desired fractions were lyophilized to give the product as a white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.82 (d, 3H, J=8Hz), 0.85 (d, 3H, J=8Hz), 1.4 (m, 9H), 2.53 (s, 3H), 3.39 (m, 2H), 4.12 (q, 1H, J=8Hz), 4.88 (m, 1H), 5.52 (m, 1H), 6.95 (s, 1H), 7.05 (m, 1H), 7.16 (m, 1H), 7.30 (m, 1H), 7.46 (m, 1H), 8.04 (s, 1H). MS (DCI/NH_3) m/e 499 $(M+H)^+$, 516 $(M+NH_4)^+$. Anal calcd for $C_{26}H_{34}N_4O_6 \cdot 1.75\ H_2O \cdot 0.65$ TFA: C, 54.27; H, 6.36; N, 9.27. Found: C, 54.18; H, 6.31; N, 9.43.

Example 76

2-[(1R)-1-[N-Phenylacetyl-Leucyl-amino]-2-(indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid

Example 76A

2-[(1R)-1-[N-Phenylacetyl-Leucyl-amino]-2-(indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid ethyl ester

The compound resulting from Example 75A (0.15 g) was taken up in 4 N HCl in dioxane (2 mL) and stirred at room temperature for 1 hour. The solvent was evaporated under reduced pressure and the residue taken up in EtOAc (10 mL). The solution was washed with saturated $NaHCO_3$ solution and brine, dried with $MgSO_4$ and evaporated *in vacuo* to give a white solid which was dissolved in THF (5 mL). Et_3N (42 μL) was added followed by phenylacetyl chloride (44 mg, 26 μL). The solution was stirred at room temperature for 5 hours. The solvent was evaporated and the residue taken up in EtOAc. The solution was washed with saturated $NaHCO_3$ solution, 1 N H_3PO_4 and brine, dried

with $MgSO_4$, and evaporated *in vacuo* to give the ethyl ester as a white solid.

Example 76B

2-{(1R)-1-[N-Phenylacetyl-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The ethyl ester resulting from Example 76A was dissolved in THF (3 mL) and a solution of LiOH (0.1 g) in H_2O (3 mL) was added. The mixture was stirred at room temperature for 18 hours. The solvent was evaporated under reduced pressure and the residue purified by preparative HPLC (Vydac μC18) eluting with a 10-70% gradient of CH_3CN in 0.1% TFA. The desired fractions were lyophilized to give the title compound as a white solid. ^1H NMR (CD_3OD, 300 MHz) δ 0.74 (d, 3H, J=8Hz), 0.77 (d, 3H, J=8Hz), 1.2-1.4 (m, 4H), 2.51 (s, 3H), 3.25-3.45 (m, 2H), 3.48 (s, 2H), 4.36 (m, 1H), 5.37 (m, 1H), 6.97 (t, 1H, J=7Hz), 7.02 (s, 1H), 7.07 (t, 1H, J=7Hz), 7.24 (m, 5H), 7.30 (d, 1H, J=9Hz), 7.46 (d, 1H, J=9Hz), 8.24 (d, 1H, J=8Hz). MS (DCI/NH_3) m/e 517 $(M+H)^+$, 534 $(M+NH_4)^+$. Anal calcd for $C_{29}H_{32}N_4O_5 \cdot 0.2$ TFA: C, 65.47; H, 6.02; N, 10.39. Found: C, 65.59; H, 6.18; N, 10.47.

Example 77

2-{(1R)-1-[N-(Benzylaminocarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared by the procedures described in Example 76 but substituting benzyl isocyanate for phenylacetyl chloride in Example 76A. ^1H NMR (CD_3OD, 300 MHz) δ 0.81 (d, 3H, J=4Hz), 0.83 (d, 3H, J=4Hz), 1.28 (t, 2H, J=8Hz), 1.45 (m, 1H), 2.51 (s, 3H), 3.46 (m, 2H), 4.23 (t, 1H, J=7Hz), 4.39 (s, 2H), 5.38 (m, 1H), 6.96 (t, 1H, J=9Hz), 7.03 (s, 1H), 7.07 (t, 1H, J=9Hz), 7.17-7.33 (m, 6H), 7.43 (d, 1H, J=9Hz). MS (DCI/NH_3) m/e 532 $(M+H)^+$, 549 $(M+NH_4)^+$. Anal calcd for $C_{29}H_{33}N_5O_5 \cdot 1.0$ TFA: C, 57.67; H, 5.31; N, 10.85. Found: C, 57.43; H, 5.08; N, 10.72.

Example 78

2-{(1R)-1-[N-(Benzenesulfonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared by the procedures described in Example 76 but substituting benzenesulfonyl chloride for phenylacetyl chloride in Example 76A. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.65 (d, 3H, J=7Hz), 0.73 (d, 3H, J=7Hz), 1.02 (m, 1H), 1.21 (m, 1H), 1.42 (m, 1H), 2.54 (s, 3H), 3.23 (t, 2H, J=7Hz), 3.55 (dd, 1H, J=6Hz,9Hz), 5.1 (m, 1H), 6.95 (dt, 1H, J=1Hz,7Hz), 7.02 (s, 1H), 7.06 (dt, 1H, J=1Hz,7Hz), 7.28 (d, 1H, J=8Hz), 7.40 (m, 4H), 7.77 (dd, 1H, J=7Hz), 8.34 (d, 7H). MS (DCI/NH_3) m/e 539 $(M+H)^+$, 556 $(M+NH_4)^+$. Anal calcd for $C_{27}H_{30}N_4SO_6 \cdot 0.2$ TFA: C, 58.62; H, 5.42; N, 9.98. Found: C, 58.70; H, 5.65; N, 10.15.

Example 79

2-{(1R)-1-[N-(N,N-Diethylaminocarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared by the procedures described in Example 76 but substituting diethylcarbamyl chloride for phenylacetyl chloride in Example 76A. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.84 (d, 6H, J=7Hz), 1.08 (t, 6H, J=7Hz), 1.42 (m, 3H), 2.54 (s, 3H), 3.26 (q, 4H, J=7Hz), 3.37 (d, 2H, J=8Hz), 4.34 (dd, 1H, J=6Hz,7Hz), 5.40 (t, 1H, J=6Hz), 6.96 (dt, 1H, J=1Hz,7Hz), 7.00 (s, 1H), 7.06 (dt, 1H, J=1Hz,7Hz), 7.30 (d, 1H, J=8Hz), 7.36 (d, 1H, J=8Hz). MS (DCI/NH_3) m/e 498 $(M+H)^+$, 515 $(M+NH_4)^+$. Anal calcd for $C_{26}H_{35}N_5O_5 \cdot 0.30$ TFA: C, 60.08; H, 6.69; N, 13.17. Found: C, 59.97; H, 6.57; N, 13.05.

Example 80

2-[(1R)-1-[N-(Cyclohexylacetyl)-Leucyl-amino]-2-(indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid

The compound resulting from Example 75A (0.10 g) was taken up in 4 N HCl in dioxane (2 mL) and stirred at room temperature for 1 hour. The solvent was evaporated under reduced pressure and the residue taken up in EtOAc (10 mL). The solution was washed with saturated $NaHCO_3$ solution and brine, dried with $MgSO_4$ and evaporated *in vacuo* to give a white solid which was dissolved in THF (5 mL). Cyclohexylacetic acid (0.03 g) was added followed by HOBt (0.03 g), N-methylmorpholine (0.02 g) and EDCI (0.04 g). DMF (1 mL) was added and the solution was stirred at room temperature for 18 hours. The solvent was evaporated and the residue taken up in EtOAc. The organic solution was washed with saturated $NaHCO_3$ solution, 1 N H_3PO_4, and brine, dried with $MgSO_4$, and evaporated. The residue was taken up in THF (2 mL). LiOH (0.10 g) in H_2O (2 mL) was added and the solution stirred at room temperature for three hours. The solvent was evaporated under reduced pressure and the residue purified by preparative HPLC (Vydac μC18) eluting with a 10-70% gradient of CH_3CN in 0.1% TFA. The desired fractions were lyophilized to give the title compound as a white solid. ^1H NMR (CD_3OD, 300 MHz) for the major diastereomer δ 0.76 (d, 3H, 7Hz), 0.78 (d, 3H, 7Hz), 0.89 (m, 3H), 1.1-1.5 (m, 7H), 1.58 (m, 6H), 2.00 (d, 2H, J=8Hz), 2.52 (s, 3H), 3.30 (m, 2H), 4.35 (m, 1H), 5.40 (m, 1H), 6.05 (m, 1H), 7.00 (s, 1H), 7.05 (m, 1H), 7.30 (d, 1H, J=7Hz), 7.44 (d, 1H, J=7Hz). MS (DCI/NH_3) m/e 522 $(M+H)^+$. Anal calcd for $C_{29}H_{39}N_5O_5 \cdot 1.25$ TFA: C, 56.97; H, 6.11; N, 10.54. Found: C, 57.10; H, 6.36; N, 10.70.

Example 81

2-{(1R)-1-[N-(2-Propylvaleryl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared following the procedures described in Example 80, substituting 2-propylpentanoic acid for cyclohexylacetic acid. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.83 (m, 12H), 1.1-1.6 (m, 11H), 2.24 (m, 1H), 2.52 (s, 3H), 3.31 (dd, 1H, J=6Hz,15Hz), 3.42 (dd, 1H, J=6Hz,15Hz), 4.41 (dd, 1H, J=6Hz,9Hz), 5.38 (m, 1H), 6.97 (dt, 1H, J=1Hz,8Hz), 7.04 (s, 1H), 7.07 (dt, 1H, J=1Hz,8Hz), 7.30 (dd, 1H, J=1Hz,7Hz), 7.46 (dd, 1H, J=1Hz,7Hz). MS (FAB) m/e 525 $(M+H)^+$, 547 $(M+Na)^+$. Anal calcd for $C_{29}H_{40}N_4O_5 \cdot 1.2\ H_2O \cdot 0.15$ TFA: C, 62.47; H, 7.61; N, 9.94. Found: C, 62.47; H, 7.64; N, 9.77.

Example 82

2-{(1R)-1-[N-(3,3-Dimethylbutyryl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared following the procedures described in Example 80, substituting 3,3-dimethylbutyric acid for cyclohexylacetic acid. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.79 (d, 3H, J=7Hz), 0.82 (d, 3H, J=7Hz), 0.96 (s,9H), 1.15-1.45 (m, 3H), 2.04 (s, 2H), 2.54 (s, 3H), 3.37 (m, 2H), 4.36 (m, 1H), 5.39 (m, 1H), 6.98 (t, 1H, J=7Hz), 7.04 (s, 1H), 7.07 (t, 1H, J=7Hz), 7.31 (d, 1H, J=7Hz), 7.46 (d, 1H, J=7Hz). MS (DCI/NH_3) m/e 497 $(M+H)^+$, 514 $(M+NH_4)^+$. Anal calcd for $C_{27}H_{36}N_4O_5 \cdot 0.35$ TFA: C, 62.19; H, 6.85; N, 10.49. Found: C, 62.17; H, 6.99; N, 10.60.

Example 83

2-{(1R)-1-[N-(Cycloheptylcarbonyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared following the procedures described in Example 80, substituting cycloheptanecarboxylic acid for cyclohexylacetic acid. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.81 (t, 6H, J=6Hz), 1.23-1.80 (m, 15H), 2.32 (m, 1H), 2.53 (s, 3H), 3.37 (m, 2H), 4.35 (m, 1H), 5.38 (dq, 1H, J=1Hz,7Hz), 6.97 (dt, 1H, J=1Hz,7Hz), 7.03 (s, 1H), 7.07 (dt, 1H, J=1Hz,7Hz), 7.30 (dd, 1H, J=1Hz,8Hz), 7.44 (dd, 1H, J=1Hz,8Hz), 8.20 (d, 1H, J=8Hz). MS (DCI/NH_3) m/e 523 $(M+H)^+$, 540 $(M+NH_4)^+$. Anal calcd for $C_{29}H_{38}N_4O_5 \cdot 0.30$ TFA: C, 63.85; H, 6.93; N, 10.06. Found: C, 63.77; H, 7.08; N, 9.90.

Example 84

2-{(1R)-1-[N-(Norborn-2-ylacetyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared following the procedures described in Example 80, substituting 2-norbornaneacetic acid for cyclohexylacetic acid and performing the saponification at 80 °C. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.81 (dd, 3H, J=2Hz,6Hz), 0.84 (dd, 3H, J=2Hz,6Hz), 1.0-1.2 (m, 4H), 1.3-1.5 (m, 7H), 1.81 (m, 1H), 1.92 (m, 1H), 1.97 (ddd, 1H, J=3Hz,8Hz,14Hz), 2.12 (22, 1H, J=9Hz,14Hz), 2.15 m, 1H), 2.53 (s, 3H), 3.3-3.5 (m, 2H), 4.37 m, 1H), 5.38 (dd, 1H, J=7Hz,8Hz), 6.97 (dt, 1H, J=1Hz,8Hz), 7.03 (s, 1H), 7.08 (dt, 1H, J=1Hz,8Hz), 7.31 (d, 1H, J=8Hz), 7.45 (dd, 1H, J=1Hz,8Hz). MS (FAB+NBA) m/e 535 $(M+H)^+$, 557 $(M+Na)^+$. Anal calcd for $C_{30}H_{38}N_4O_5 \cdot 0.8$ TFA: C, 60.64; H, 6.25; N, 8.95. Found: C, 60.26; H, 6.39; N, 8.98.

Example 85

2-{(1R)-1-[N-(4-Methoxyphenylacetyl)-Leucyl-amino]-2-(indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared following the procedures described in Example 80, substituting 4-methoxyphenylacetic acid for cyclohexylacetic acid and performing the saponification at 80 °C. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.76 (d, 3H, J=6Hz), 0.79 (d, 3H, J=6Hz), 1.3-1.4 (m, 3H), 2.50 (s, 3H), 3.2-3.4 (m, 2H), 3.41 (m, 2H), 3.73 (s, 3H), 4.37 (m, 1H), 5.35 (dd, 1H, J=7Hz,8Hz), 6.79 (td, 2H, J=2Hz,9Hz), 6.97 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.00 (s, 1H), 7.08 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.12 (td, 2H, J=2Hz,9Hz), 7.32 (d, 1H, J=8Hz), 7.44 (dd, 1H, J=1Hz,8Hz). MS (DCI/NH_3) m/e 547 $(M+H)^+$, 564 $(M+NH_4)^+$. Anal calcd for $C_{30}H_{34}N_4O_6 \cdot 0.7$ TFA: C, 60.21; H, 5.58; N, 8.94. Found: C, 60.30; H, 5.47, N; 9.28.

Example 86

2-{(1R)-1-[(N-Cbz-Leucyl)-amino]-2-(indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared following the procedures described in Example 75, substituting Cbz-Leu-OH for Boc-Leu-OH·H_2O in Example 75A. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.91 (t, 6H, J=7Hz), 0.78-1.74 (m, 11H), 2.35 (s, 3H), 3.20 (s, 3H), 3.38 (m, 4H), 3.50 (m, 2H), 4.27 (dd, 1H, J=5Hz,7Hz), 5.36 (dd, 1H, J=5Hz,7Hz), 6.96 (t, 1H, J=7Hz), 7.07 (s, 1H), 7.09 (t, 1H, J=7Hz), 7.27 (d, 1H, J=7), 7.34 (d, 1H, J=7Hz). MS (FAB) m/e 537 $(M+H)^+$, 599 $(M+Na)^+$. Anal calcd for $C_{29}H_{40}N_6O_4 \cdot 1.25$ TFA · 1.75 H_20: C, 53.24; H, 6.35; N, 11.82. Found: C, 52.83; H, 5.95; N, 12.46.

Example 87

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-4-trifluoromethyl-oxazole-5-carboxylic acid

Example 87A

Boc-D-(N$_i$-methyl)Tryptophanyl-NH_2

A solution of 0.955 g (3.0 mmol) of Boc-D-Trp(1-Me)-OH, prepared according to the method of Cook, *et al.*, Chem. Pharm. Bull. 13 88 (1965), in 25 mL of THF was cooled to -20 °C. N-Methylmorpholine (0.33 mL, 1.0 eq) was added, followed by 0.39 mL (1.0 eq) of isobutyl chloroformate. The resultant slurry was stirred for 30 minutes, followed by the addition of a solution of 0.2 mL of concentrated ammonia in 3 mL of THF. The mixture was warmed slowly to 0 °C over 1 hour. The solvents were removed *in vacuo*, and the residue was taken up in ethyl acetate, washed sequentially with water, saturated sodium bicarbonate solution, 1 N H_3PO_4 and brine, dried, and concentrated *in vacuo* to afford 0.95 g (100% yield) of the title compound as a white foam.

Example 87B

2-{(1R)-1-(Boc-Amino)-2-(1-methyl-indol-3-yl)ethyl}-4-trifluoromethyl-oxazole-5-carboxylic acid ethyl ester

The compound resulting from Example 87A (92 mg, 0.3 mmol) was combined with 66 mg of ethyl 2-chloro trifluoroacetoacetate and 0.3 mL of propylene oxide in 1 mL of THF; the solution was heated at 110 °C for 6 hours. The solvents were removed *in vacuo*; and the crude product was purified by flash chromatography on silica gel eluting with 2:1 hexanes-ethyl acetate to give 102 mg of the hydrated condensation product. This material was dissolved in 2 mL of pyridine, cooled to 0 °C and 4 drops of trifluoracetic anhydride were added. The mixture was allow to warm to ambient temperature and stirred for 4 hours. The solvents were removed *in vacuo*, and the product was purified by flash chromatography on silica gel eluting with 3:1 hexanes-

ethyl acetate to afford 57.5 mg (40%) of the title compound as a yellowish oil.

Example 87C

2-[(1R)-1-Amino-2-(1-methyl-indol-3-yl)ethyl]-4-trifluoromethyl-oxazole-5-carboxylic acid ethyl ester

The compound resulting from Example 87B (50 mg) was dissolved in 3 mL of trifluoroacetic acid and stirred at ambient temperature for 45 minutes. The solvents were removed *in vacuo*, and the residue was taken up in saturated sodium bicarbonate solution and extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 and stripped *in vacuo* to give a crude product which was used without further purification.

Example 87D

2-[(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-4-trifluoromethyl-oxazole-5-carboxylic acid

The compound resulting from Example 87C (40 mg) was dissolved in THF (1 mL). HOBt (15 mg), the acid prepared in Example 57D (30 mg) and EDCI (21 mg) were added. N-Methylmorpholine (10 µL) was added and the mixture stirred at room temperature for 18 hours. The solvent was evaporated under reduced pressure and the residue taken up in EtOAc. The solution was washed with saturated $NaHCO_3$ solution, 1 N H_3PO_4 and brine, dried with $MgSO_4$, and evaporated *in vacuo* to give an yellowish oil.

To this compound dissolved in THF (2 mL) was added a solution of LiOH (50 mg) in H_2O (1 mL) and the mixture stirred at room temperature for 15 hours. The solvents were evaporated under reduced pressure and the residue purified by preparative HPLC (Vydac µC18) eluting with a 10-70% gradient of CH_3CN in 0.1% TFA. The desired fractions were lyophilized to give the product as a white solid. ^1H NMR (CD_3OD, 300 MHz) δ 0.84 (d, 3H, J=7Hz), 0.85 (d, 3H, J=7Hz), 1.40 (m, 2H), 1.52 (m, 5H), 1.67 (m, 4H), 3.3-3.5 (m, 6H), 3.75 (s, 3H), 4.31 (dd,

1H, J=5Hz,10Hz), 5.43 (dd, 1H, J=7Hz,8Hz), 7.00 (s, 1H), 7.01 (m, 1H), 7.14 (dt, 1H, J=1Hz,8Hz), 7.30 (td, 1H, J=1Hz,8Hz), 7.43 (td, 1H, J=1Hz,8Hz). MS (FAB+NBA) m/e 592 $(M+H)^+$, 614 $(M+Na)^+$, 630 $(M+K)^+$. Anal calcd for $C_{29}H_{36}F_3N_5O_5 \cdot 0.7$ TFA: C, 54.38; H, 5.51; N, 10.43. Found: C, 54.50; H, 5.54; N, 10.51.

Example 88

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-oxazole-4-carboxylic acid

The title compound was prepared following the procedures described in Example 87, substituting ethyl bromopyruvate for ethyl 2-chlorotrifluoroacetoacetate in Example 87B. ^1H NMR (CD_3OD, 300 MHz) δ 0.84 (d, 6H, J=7Hz), 1.40 (m, 2H), 1.52 (m, 5H), 1.68 (m, 4H), 3.3-3.5 (m, 6H), 3.72 (d, 3H, J=4Hz), 4.34 (dd, 1H, J=5Hz,10Hz), 5.46 (ddd, 1H, J=1Hz,7Hz,8Hz), 6.96 (d, 1H, J=4Hz), 7.01 (m, 1H), 7.14 (m, 1H), 7.28 (dd, 1H, J=5Hz,8Hz), 7.45 (m, 1H), 8.35 (s, 1H). MS (FAB+NBA) m/e 524 $(M+H)^+$, 546 $(M+Na)^+$, 546 $(M+Cu)^+$. Anal calcd for $C_{28}H_{37}N_5O_5 \cdot 0.55$ TFA: C, 59.61; H, 6.46; N, 11.94. Found: C, 59.57; H, 6.49; N, 11.95.

Example 89

2-{(1R)-1-[N-(Homopiperidin-1-ylcarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-oxazole-5-carboxylic acid

The title compound was prepared following the procedures described in Example 87, substituting ethyl bromopyruvate for ethyl 2-chlorotrifluoroacetoacetate in Example 87B and replacing trifluoroacetic anhydride with methanesulfonyl chloride/triethylamine as the dehydrating agent. ^1H NMR (CD_3OD, 300 MHz) δ 0.84 (d, 3H, J=7Hz), 0.91 (d, 3H, J=7Hz), 1.4 (m, 2H), 1.52 (m, 5H), 1.67 (m, 4H), 3.2-3.5 (m, 6H), 3.73 (s, 3H), 4.34 (m, 1H), 5.46 (dd, 1H, J=7Hz,8Hz), 6.97 (s, 1H), 7.03 (dt, 1H, J=1Hz,8Hz), 7.13 (m, 1H), 7.28 (d, 1H, J=8Hz), 7.53 (dd, 1H, J=1Hz,8Hz), 7.65 (s, 1H). MS (FAB+NBA) m/e 524 $(M+H)^+$. HRMS Calcd for $C_{28}H_{38}N_5O_5$: 524.2873. Found: 524.2858 .

Example 90

2-[(1R)-1-[N-(*exo*-2-Norbornylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid

Example 90A

Boc-D-(1-methyl)-Tryptophanyl-(2-acetylGlycine)-benzyl ester

N-(Diphenylmethylene)glycine benzyl ester (14.25 g) was dissolved in THF (175 mL) and the solution cooled to -78 °C. Lithium hexamethyldisilazide (43.25 mL, 1 N solution in THF) was added slowly over 15 minutes, and the resulting yellow slurry stirred at -78 °C for 45 minutes. The slurry was then transferred via cannula to a solution of acetyl chloride (3.4 mL) in THF (125 mL) at -78 °C. Complete transfer of the anion took about 30 minutes. After the addition was complete, the reaction was stirred at -78 °C for 30 minutes then allowed to warm to room temperature and stirred an additional three hours. The reaction was then quenched with 2 N HCl (50 mL). The THF was evaporated, and the resulting aqueous solution was washed with EtOAc (2 x 50 mL). The organic phases were discarded and the aqueous phase was concentrated *in vacuo*. The resulting slurry was treated with EtOH (100 mL) and the insolubles filtered off. The filtrate was evaporated to give 2-acetylglycine benzyl ester hydrochloride as a yellow solid (10.48 g, 99%) which was used without further purification.

Boc-D-(1-Methyl)-tryptophan (10.0 g) was dissolved in THF (75 mL) and the solution cooled to -20 °C. N-Methylmorpholine (3.45 mL) was added followed by the dropwise addition of isobutylchloroformate (4.0 mL). The 2-acetylglycine ester from above was dissolved in DMF (60 mL) and added to the mixed anhydride at -20 °C. N-Methylmorpholine (3.5 mL) was then added via syringe pump over a one hour period. After the addition was complete, the reaction was allowed to stir at room temperature for one hour. Water (250 mL) was added and the mixture extracted with EtOAc (2 x 100 mL). The organic layer was washed with saturated $NaHCO_3$ solution, 1 N H_3PO_4 and

brine, dried with $MgSO_4$, and evaporated under reduced pressure to give a yellow oil which was purified by flash chromatography on silica gel eluting with 40% EtOAc-hexane. The product was isolated as a yellow oil (7.50 g, 47% yield). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.43 (s, 9H), 2.18 (s, 1.5H), 2.24 (s, 1.5H), 3.17 (m, 1H), 3.20 (m, 1H), 3.74 (s, 3H), 4.50 (br s, 1H), 5.15 (m, 3H), 6.93 (d, 1H, J=7Hz), 7.11 (t, 1H, J=7Hz), 7.22 (t, 1H, J=7Hz), 7.33 (m, 6H), 7.59 (t, 1H, J=7Hz). MS (DCI/NH_3) m/e 508 $(M+H)^+$, 525 $(M+NH_4)^+$.

Example 90B

2-{(1R)-1-(Boc-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid benzyl ester

The compound resulting from Example 90A (7.25 g) was dissolved in pyridine (25 mL), acetonitrile (25 mL), and carbon tetrachloride (3 mL). DBU (4.5 mL) and triphenylphosphine (4.20 g) were added and the mixture stirred at ambient temperature for 18 hours. The solvents were evaporated and the residue taken up in EtOAc (50 mL), washed with saturated $NaHCO_3$ solution, 1 N H_3PO_4, and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The resulting yellow oil was purified by flash chromatography on silica gel eluting with 30% EtOAc-hexane to give a pale yellow solid (4.35 g, 63%). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.40 (s, 9H), 2.48 (s, 3H), 3.36 (m, 2H), 3.61 (s, 3H), 5.20 (m, 2H), 5.35 (s, 2H), 6.78 (br s, 1H), 7.03 (t, 1H, J=7Hz), 7.18 (t, 1H, J=7Hz), 7.24 (d, 1H, J=7Hz), 7.40 (m, 6H). MS (DCI/NH_3) m/e 490 $(M+H)^+$, 507 $(M+NH_4)^+$.

Example 90C

2-{(1R)-1-Amino-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid benzyl ester

The compound resulting from Example 90B (120 mg) was dissolved in 6 mL of trifluoroacetic acid and allowed to stir at ambient temperature for 1 hour. The solvents were removed *in vacuo*, the residue was neutralized with bicarbonate solution, and the mixture was

extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was used without further purification.

Example 90D

N-(*exo*-2-Norbornylaminocarbonyl)-Leucyl-OH

Leucyl-OBn · pTsOH (1.97 g, 5.0 mmol) was suspended in 10 mL of THF, Et_3N (0.8 mL) was added, and the resultant solution was cooled to 0 °C in an ice bath. Carbonyldiimidazole (0.85 mg) was added, the bath was removed, and the solution was allowed to warm to room temperature over 2 hours. (±)-*exo*-2-Aminonorbornane (0.61 mL, 5.1 mmol) was added and the solution stirred overnight at room temperature. The solution was washed with saturated $NaHCO_3$ solution, 1 N H_3PO_4 and brine, dried with $MgSO_4$, and evaporated under reduced pressure to give a white solid which was used without further purification.

The ester was dissolved in EtOH (100 mL), 10% Pd/C (200 mg) was added and the mixture stirred under hydrogen for 5 hours. The solvent was removed *in vacuo* and the residue taken up in EtOAc and filtered through Celite® to remove the catalyst. The solvent was evaporated *in vacuo* to give the carboxylic acid as a white solid (1.29 g, 96%).

Example 90E

2-[(1R)-1-[N-(*exo*-2-Norbornylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid benzyl ester

The crude compound resulting from Example 90C was dissolved in THF (2 mL). HOBt (42 mg), the acid resulting from Example 90D (80 mg) and EDCI (57 mg) were added. N-Methylmorpholine (100 µL) was added and the mixture stirred at room temperature for 18 hours. The solvent was evaporated under reduced pressure and the residue taken up in EtOAc. The solution was washed with saturated $NaHCO_3$ solution, 1 N H_3PO_4 and brine, dried with $MgSO_4$, and evaporated *in vacuo* to

give an orange oil which was purified by flash chromatography on silica gel eluting with 50% EtOAc-hexane.

Example 90F

2-[(1R)-1-[N-(*exo*-2-Norbornylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid

The product resulting from Example 90E was dissolved in 30 mL of EtOH, 50 mg of 10% palladium on carbon was added, and the mixture was purged with nitrogen. The nitrogen line was exchanged for a balloon of hydrogen, and the mixture was stirred at ambient temperature for 4 hours. The catalyst was removed by filtration through a pad of Celite; the solvents were removed *in vacuo*. The crude material was triturated with ether/hexanes, dissolved in 0.1% aqueous TFA/acetonitrile, and lyophilized to give the title compound as a white powder (96 mg). ^{1}H NMR (CD_3OD, 300 MHz) of one diastereomer δ 0.81 (d, 3H, J=6Hz), 0.83 (d, 3H, J=6Hz), 1.1-1.5 (m, 10H), 1.70 (m, 1H), 2.08 (m, 1H), 2.22 (m, 1H), 2.53 (s, 3H), 3.3-3.5 (m, 3H), 3.72 (s, 3H), 4.19 (t, 1H, J=7Hz), 5.37 (ddd, 1H, J=2,6,8Hz), 6.99 (s, 1H), 7.00 (dt, 1H, J=1,7Hz), 7.12 (dt, 1H, J=1,7Hz), 7.20 (d, 1H, J=8Hz), 7.44 (dd, 1H, J=1,8Hz). MS (FAB/NBA) m/e 550 $(M+H)^+$, 572 $(M+Na)^+$. Anal calcd for $C_{30}H_{39}N_5O_5 \cdot 0.3$ TFA: C, 62.95; H, 6.78; N, 11.99. Found: C, 62.70; H, 6.86; N, 11.98.

Example 91

2-[(1R)-1-[N-(*endo*-2-Norbornylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared following the procedures described in Example 90, substituting (±)-*endo*-2-aminonorbornane for (±)-*exo*-2-aminonorbornane in Example 90D. The crude material was purified by trituration with ether; the resultant material was dissolved in 0.1% aqueous TFA in acetonitrile and lyophilized to give the title compound as a white powder (109 mg). ^{1}H NMR (CD_3OD, 300 MHz) of one diastereomer δ 0.81 (d, 3H, J=6Hz), 0.84 (d, 3H, J=6Hz), 1.1-1.6

(m, 10H), 1.99 (m, 1H), 2.15 (m, 1H), 2.32 (m, 1H), 2.54 (s, 3H), 3.35 (m, 2H), 3.73 (s, 3H), 3.86 (m, 1H), 4.20 (dt, 1H, J=1Hz,7Hz), 5.36 (dd, 1H, J=6Hz,8Hz), 6.97 (s, 1H), 7.00 (dt, 1H, J=1Hz,7Hz), 7.12 (t, 1H, J=7Hz), 7.28 (d, 1H, J=8Hz), 7.44 (d, 1H, J=8Hz). MS (FAB/NBA) m/e 550 $(M+H)^+$, 572 $(M+Na)^+$. Anal calcd for $C_{30}H_{39}N_5O_5 \cdot 0.5$ TFA: C, 61.37; H, 6.56; N, 11.54. Found: C, 61.11; H, 6.78; N, 11.92.

Example 92

2-{(1R)-1-[N-(N-Cyclohexylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared following the procedures described in Example 90, substituting cyclohexylamine for (±)-*exo*-2-aminonorbornane in Example 90D. The crude product was triturated with diethyl ether/hexanes, dissolved in acetonitrile and 0.1% aqueous TFA, and lyophilized to give the product as a white powder. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.70 (d, 3H, J=7Hz), 0.74 (d, 3H, J=7Hz), 1.1-1.9 (m, 13H), 2.50 (s, 3H), 3.40 (m, 1H), 3.76 (s, 3H), 3.90 (m, 1H), 4.35 (dd, 1H, J=6,7), 5.35(m, 1H), 6.91 (s, 1H), 7.02 (t, 1H, J=8Hz), 7.13 (t, 1H, J=8Hz), 7.32 (d, 1H, J=8Hz), 7.48 (d, 1H, J=8Hz). MS (FAB/NBA) m/e 538 $(M+H)^+$, 560 $(M+Na)^+$, 576 $(M+K)^+$. Anal calcd for $C_{29}H_{39}N_5O_5 \cdot 0.6$ TFA: C, 59.85 H, 6.59; N, 11.56. Found: C, 59.82; H, 6.61; N, 11.66.

Example 93

2-{(1R)-1-[N-(N-Methyl-N-cyclohexylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared following the procedures described in Example 90, substituting N-methylcyclohexylamine for (±)-*exo*-2-aminonorbornane in Example 90D. The crude product was triturated with diethyl ether/hexanes, dissolved in acetonitrile and water, and lyophilized to give the product as a white powder. ^1H NMR (CD_3OD, 300 MHz) δ 0.71 (d, 3H, J=7Hz), 0.73 (d, 3H, J=7Hz), 1.1-1.8 (m, 13H), 2.54 (s, 3H), 2.71 (s, 3H), 3.45 (m, 1H), 3.72 (s, 3H), 3.90 (m, 1H), 4.32 (dd, 1H, J=6,7), 5.38 (m, 1H), 6.92 (s, 1H), 7.0 (t, 1H, J=8Hz),

7.13 (t, 1H, J=8Hz), 7.30 (d, 1H, J=8Hz), 7.52 (d, 1H, J=8Hz). MS (FAB/NBA) m/e 552 $(M+H)^+$. Anal calcd for $C_{30}H_{41}N_5O_5 \cdot 1.0\ H_2O$: C, 63.25; H, 7.61; N, 12.29. Found: C, 63.19; H, 7.45; N, 12.33.

Example 94

2-{(1R)-1-[N-(N-Ethyl-N-cyclohexylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared following the procedures described in Example 90, substituting N-ethylcyclohexylamine for (±)-*exo*-2-aminonorbornane in Example 90D. The residue was triturated with 1:1 hexanes/ether; the resultant material was dissolved in 0.1% aqueous TFA in acetonitrile and lyophilized to give the title compound as a white powder (30 mg). ^1H NMR (CD_3OD, 300 MHz) δ 0.83 (d, 3H, J=6Hz), 0.84 (d, 3H, J=6Hz), 1.07 (t, 3H, J=7Hz), 1.3-1.8 (m, 13H), 2.52 (s, 3H), 3.08 (q, 2H, J=7Hz), 3.3-3.4 (m, 2H), 3.72 (s, 3H), 3.87 (m, 1H), 4.36 (dd, 1H, J=6,10Hz), 5.38 (dd, 1H, J=7,8Hz), 6.94 (s, 1H), 7.00 (dt, 1H, J=1,7Hz), 7.12 (dt, 1H, J=1,7Hz), 7.29 (d, 1H, J=8Hz), 7.42 (d, 1H, J=8Hz). MS (DCI/NH_3) m/e 566 $(M+H)^+$. Anal calcd for $C_{31}H_{43}N_5O_5 \cdot 0.5$ TFA: C, 61.72; H, 7.04; N, 11.25. Found: C, 61.89; H, 7.13; N, 11.26.

Example 95

2-{(1R)-1-[N-(N-Propyl-N-cyclohexylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared following the procedures described in Example 90, substituting N-propylcyclohexylamine for (±)-*exo*-2-aminonorbornane in Example 90D. The crude final product was purified by preparative HPLC (Vydac μC18) eluting with a 20-90% gradient of CH_3CN in 0.1% TFA. The desired fractions were lyophilized to give the title compound as a white solid (66 mg). ^1H NMR (CD_3OD, 300 MHz) δ 0.83 (d, 3H, J=6Hz), 0.84 (d, 3H, J=6Hz), 0.86 (t, 3H, J=7Hz), 1.3-1.8 (m, 15H), 2.52 (s, 3H), 3.04 (m, 2H), 3.3-3.4 (m, 2H), 3.73 (s, 3H), 4.35 (dd, 1H, J=5Hz,9Hz), 5.38 (dd, 1H, J=7Hz,8Hz), 6.94 (s, 1H), 7.00 (dt, 1H, J=1Hz,7Hz), 7.13 (dt, 1H, J=1Hz,7Hz), 7.29 (d, 1H,

J=8Hz), 7.43 (d, 1H, J=8Hz). MS (DCI/NH_3) m/e 580 $(M+H)^+$. Anal calcd for $C_{32}H_{45}N_5O_5 \cdot 1.0$ TFA: C, 58.87; H, 6.68; N, 10.09. Found: C, 58.85; H, 6.75; N, 10.20.

Example 96

2-[(1R)-1-[N-(*trans*-4-Hydroxycyclohexylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared following the procedures described in Example 90, substituting *trans*-4-hydroxycyclohexylamine for (±)-*exo*-2-aminonorbornane in Example 90D. The crude final product was purified by trituration with 15:1 EtOAc-MeOH; the resultant material was dissolved in 0.1% aqueous TFA in acetonitrile and lyophilized to give the title compound as a white powder (131 mg). ^1H NMR (CD_3OD, 300 MHz) δ 0.81 (d, 3H, J=6Hz), 0.83 (d, 3H, J=6Hz), 1.1-1.5 (m, 7H), 1.8-2.0 (m, 4H), 2.53 (s, 3H), 3.3-3.6 (m, 3H), 3.56 (dd, 1H, J=7Hz,15Hz), 3.73 (s, 3H), 4.18 (t, 1H, J=7Hz), 5.36 (dd, 1H, J=6Hz,8Hz), 6.97 (s, 1H), 7.01 (ddd, 1H, J=1Hz,7Hz,8Hz), 7.13 (dt, 1H, J=1Hz,7Hz), 7.29 (d, 1H, J=8Hz), 7.45 (d, 1H, J=8Hz). MS (FAB/MeOH) m/e 554 $(M+H)^+$, 576 $(M+Na)^+$. Anal calcd for $C_{29}H_{39}N_5O_5 \cdot 1.2$ TFA · 2 H_2O: C, 51.91; H, 6.13; N, 9.64. Found: C, 51.48; H, 5.90; N, 9.92.

Example 97

2-[(1R)-1-[N-(2-Methylcyclohexylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared following the procedures described in Example 90, substituting 2-methylcyclohexylamine for (±)-*exo*-2-aminonorbornane in Example 90D. The crude product was purified by preparative HPLC (Vydac μC18) eluting with a 10-70% gradient of CH_3CN in 0.1% TFA. The appropriate fraction was lyophilized to give the product as a white solid. ^1H NMR (CD_3OD, 300 MHz) consistent with structure of the four isomers δ 2.52 (s, 3H), 3.74 (s, 3H), 6.97 (s, 1H), 7.0 (t, 1H, J=8Hz), 7.13 (t, 1H, J=8Hz), 7.30 (d, 1H, J=8Hz), 7.45 (dd, J=2,8Hz). MS (DCI/NH_3) m/e 552 $(M+H)^+$, 569

$(M+NH_4)^+$. Anal calcd for $C_{30}H_{41}N_5O_5 \cdot 1.0\ H_2O \cdot 0.35$ TFA: C, 60.55; H, 7.15; N, 11.33. Found: C, 60.49; H, 7.17; N, 11.49.

Example 98

2-{(1R)-1-[N-(3-Methylcyclohexylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared following the procedures described in Example 90, substituting 3-methylcyclohexylamine for (±)-*exo*-2-aminonorbornane in Example 90D. The crude product was purified by preparative HPLC (Vydac μC18) eluting with a 10-70% gradient of CH_3CN in 0.1% TFA. The appropriate fraction was lyophilized to give the product as a white solid. ^1H NMR (CD_3OD, 300 MHz) consistent with structure of the four isomers δ 2.52 (s, 3H), 3.74 (s, 3H), 6.97 (s, 1H), 7.0 (t, 1H, J=8Hz), 7.13 (t, 1H, J=8Hz), 7.30 (d, 1H, J=8Hz), 7.45 (dd, J=2,8Hz). MS (DCI/NH_3) m/e 552 $(M+H)^+$, 569 $(M+NH_4)^+$. Anal calcd for $C_{30}H_{41}N_5O_5 \cdot 1.1\ H_2O \cdot 0.65$ TFA: C, 58.39; H, 6.83; N, 10.88. Found: C, 58.43; H, 6.82; N, 10.87.

Example 99

2-{(1R)-1-[N-(4-Methylcyclohexylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared following the procedures described in Example 90, substituting 4-methylcyclohexylamine for (±)-*exo*-2-aminonorbornane in Example 90D. The crude product was triturated with diethyl ether/hexanes, dissolved in acetonitrile and 0.1% aqueous TFA, and lyophilized to give the product as a white powder. ^1H NMR ($CDCl_3/CD_3OD$, 300 MHz) consistent with structure of the four isomers δ 2.52 (s, 3H), 3.73 (s, 3H), 6.95 (s, 1H), 7.02 (dt, 1H, J=1,8Hz), 7.16 (dt, 1H, J=1,8Hz), 7.27 (d, 1H, J=8Hz), 7.41 (d, J=8Hz). MS (DCI/NH_3) m/e 552 $(M+H)^+$, 569 $(M+NH_4)^+$. Anal calcd for $C_{30}H_{41}N_5O_5 \cdot 0.3\ H_2O \cdot 0.75$ TFA: C, 58.88; H, 6.64; N, 10.90. Found: C, 58.80; H, 6.45; N, 11.05.

Example 100

2-[(1R)-1-[N-(Cyclopentylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared following the procedures described in Example 90, substituting cyclopentylamine for (±)-*exo*-2-aminonorbomane in Example 90D. The crude product was triturated with diethyl ether/hexanes, dissolved in acetonitrile and 0.1% aqueous TFA, and lyophilized to give the product as a white powder. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.70 (d, 3H, J=7Hz), 0.74 (d, 3H, J=7Hz), 1.1-1.8 (m, 11H), 2.52 (s, 3H), 3.44 (m, 1H), 3.75 (s, 3H), 3.89 (m, 1H), 4.42 (dd, 1H, J=6Hz,7Hz), 5.35 (m, 1H), 6.96 (s, 1H), 7.03 (t, 1H, J=8Hz), 7.12 (t, 1H, J=8Hz), 7.30 (d, 1H, J=8Hz), 7.45 (d, 1H, J=8Hz). MS (FAB/NBA) m/e 524 $(M+H)^+$, 546 $(M+Na)^+$, 562 $(M+K)^+$. Anal calcd for $C_{28}H_{37}N_5O_5 \cdot 1.0\ H_2O \cdot 0.5$ TFA: C, 58.18; H, 6.65; N, 11.70. Found: C, 58.31; H, 6.61; N, 11.70.

Example 101

2-[(1R)-1-[N-(Cycloheptylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared following the procedures described in Example 90, substituting cycloheptylamine for (±)-*exo*-2-aminonorbomane in Example 90D. The crude product was triturated with diethyl ether/hexanes, dissolved in acetonitrile and 0.1% aqueous TFA, and lyophilized to give the product as a white powder. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.73 (d, 3H, J=7Hz), 0.77 (d, 3H, J=7Hz), 1.3-1.8 (m, 15H), 2.50 (s, 3H), 3.45(m, 1H), 3.75 (s, 3H), 3.92 (m, 1H), 4.45 (dd, 1H, J=6,7), 5.35 (m, 1H), 6.95 (s, 1H), 7.02 (t, 1H, J=8Hz), 7.12 (t, 1H, J=8Hz), 7.30 (d, 1H, J=8Hz), 7.45 (d, 1H, J=8Hz). MS (FAB/NBA) m/e 552 $(M+H)^+$, 574 $(M+Na)^+$, 590 $(M+K)^+$. Anal calcd for $C_{30}H_{41}N_5O_5 \cdot 1.0\ H_2O \cdot 0.3$ TFA: C, 60.86; H, 7.23; N, 11.60. Found: C, 60.86; H, 7.20; N, 11.62.

Example 102

2-[(1R)-1-[N-(1-Piperidinylcarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared following the procedures described in Example 90, substituting piperidine for (±)-*exo*-2-aminonorbornane in Example 90D. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.89 (d, 3H, J=7Hz), 0.90 (d, 3H, J=7Hz), 1.4-1.7 (m, 3H), 2.50 (s, 3H), 3.3-3.4 (m, 2H), 3.53 (s, 3H), 4.52 (dd, 1H, J=6Hz,10Hz), 5.43 (dd, 1H, J=7Hz,8Hz), 6.62 (d, 1H, J=4Hz), 6.89-6.96 (m, 2H), 7.06 (dt, 1H, J=1Hz,8Hz), 7.14-7.30 (m, 3H), 7.36 (d, 1H, J=7Hz), 7.57 (dd, 1H, J=1Hz,7Hz), 7.65 (d, 1H, J=4Hz), 8.16 (dd, 1H, J=1Hz,7Hz). MS (DCI/NH_3) m/e 556 $(M+H)^+$, 573 $(M+NH_4)^+$. Anal calc for $C_{31}H_{33}N_5O_5 \cdot 0.9$ TFA: C, 59.85; H, 5.19; N, 10.64. Found: C, 60.15; H, 5.46; N, 10.49.

Example 103

2-[(1R)-1-[N-(4-Morpholinylcarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared following the procedures described in Example 90, substituting morpholine for (±)-*exo*-2-aminonorbornane in Example 90D. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.83 (d, 3H, J=6Hz), 0.84 (d, 3H, J=6Hz), 1.2-1.6 (m, 3H), 2.55 (s, 3H), 3.2-3.4 (m, 6H), 3.58 (t, 4H, J=6Hz), 3.73 (s, 3H), 4.30 (dd, 1H, J=6Hz,9Hz), 5.39 (dd, 1H, J=7Hz,8Hz), 6.95 (s, 1H), 7.00 (dt, 1H, J=1Hz,8Hz), 7.14 (dt, 1H, J=1Hz,8Hz), 7.35 (d, 1H, J=8Hz), 7.44 (d, 1H, J=8Hz). MS (DCI/NH_3) m/e 526 $(M+H)^+$, 543 $(M+NH_4)^+$. Anal calcd for $C_{27}H_{35}N_5O_6 \cdot 1.0$ TFA: C, 54.46; H, 5.67; N, 10.95. Found: C, 54.41; H, 5.75; N, 10.74.

Example 104

2-[(1R)-1-[N-(1-Carbomethoxycyclohexylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared following the procedures described in Example 90, substituting 1-carbomethoxycyclohexylamine for (±)-*exo*-2-aminonorbornane in Example 90D. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.81 (d, 3H, J=7Hz), 0.82 (d, 3H, J=7Hz), 1.24-1.34 (m, 3H), 1.40-1.65 (m, 6H), 1.67-1.81 (m, 2H), 1.89-1.99 (m, 2H), 2,53 (s, 3H), 3.2-3.45 (m, 2H), 3.60 (s, 3H), 3.74 (s, 3H), 4.15 (dd, 1H, J=6Hz,8Hz), 5.35 (dd, 1H, J=6Hz,8Hz), 6.97-7.04 (m, 2H), 7.13 (dt, 1H, J=1Hz,8Hz), 7.3 (d, 1H, J=8Hz), 7.45 (d, 1H, J=8Hz). MS (DCI/NH_3) m/e 595 $(M+H)^+$. Anal calcd for $C_{31}H_{41}N_5O_5 \cdot 0.7$ TFA: C, 57.61; H, 6.22; N, 10.37. Found: C, 57.73; H, 6.48; N, 10.28.

Example 105

2-[(1R)-1-[N-(1,2,3,4-Tetrahydronaphth-1-ylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared following the procedures described in Example 90, substituting 1-amino-1,2,3,4-tetrahydronaphthylene for (±)-*exo*-2-aminonorbornane in Example 90D. ^{1}H NMR (CD_3OD, 300 MHz) of major isomer δ 0.83 (d, 6H, J=6Hz), 1.2-1.6 (m, 3H), 1.6-2.0 (m, 4H), 2.53 (s, 3H), 2.7-2.8 (m, 2H), 3.2-3.4 (m, 3H), 3.74 (s, 3H), 4.27 (m, 1H,), 5.40 (m, 1H), 6.9-7.2 (m, 7H), 7.26 (d, 1H, J=8Hz), 7.45 (m, 1H). MS (DCI/NH_3) m/e 586 $(M+H)^+$, 603 $(M+NH_4)^+$. Anal calcd for $C_{33}H_{39}N_5O_5 \cdot 0.4$ TFA: C, 64.31; H, 6.29; N, 11.09. Found: C, 64.24; H, 6.62; N, 10.70.

Example 106

2-{(1R)-1-[N-(1-Adamantylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared following the procedures described in Example 90, substituting 1-adamantylamine for (±)-*exo*-2-aminonorbornane in Example 90D. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.82 (d, 3H, J= 6Hz), 0.83 (d, 3H, J=6Hz), 1.2-1.55 (m, 3H), 1.69 (m, 6H), 1.91 (d, 6H, J=3Hz), 1.92-2.07 (m, 3H), 2.53 (s, 3H), 3.2-3.4 (m, 2H), 3.74 (s, 3H), 4.13 (dd, 1H, J=6Hz,9Hz), 5.36 (dd, 1H, J=6Hz,8Hz), 6.98 (s, 1H), 7.01 (dt, 1H, J=1Hz,8Hz), 7.13 (dt, 1H, J=1Hz,8Hz), 7.23 (d, 1H, J=8Hz), 7.43 (d, 1H, J=8Hz). MS (DCI/NH_3) m/e 590 $(M+H)^+$, 607 $(M+NH_4)^+$. Anal calcd for $C_{33}H_{43}N_5O_5 \cdot 0.7$ TFA: C, 61.71; H, 6.58; N, 10.46. Found: C, 61.52; H, 6.59; N, 10.75.

Example 107

2-{(1R)-1-[N-(2-Adamantylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared following the procedures described in Example 90, substituting 2-adamantylamine for (±)-*exo*-2-aminonorbornane in Example 90D. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.83 (d, 3H, J= 6Hz), 0.84 (d, 3H, J=6Hz), 1.3 (m 2H), 1.45 (m, 1H), 1.5-1.65 (m, 3H), 1.7-1.8 (m, 11H), 2.53 (s, 3H), 3.25-3.4 (m, 2H), 3.73 (s, 3H) 3.76 (br s, 1H), 4.20 (dd, 1H, J=6Hz,8Hz), 5.38 (dd, 1H, J=6Hz,8Hz), 6.97 (s, 1H), 7.01 (dt, 1H, J=1Hz,8Hz), 7.14 (dt, 1H, J=1Hz,8Hz), 7.28 (d, 1H, J=8Hz), 7.45 (d, 1H, J=8Hz). MS (DCI/NH_3) m/e 590 $(M+H)^+$, 607 $(M+NH_4)^+$. Anal calcd for $C_{33}H_{43}N_5O_5 \cdot 0.8$ TFA: C, 61.03, H, 6.48; N, 10.28. Found: C, 61.23; H, 6.74; N, 10.39.

Example 108

2-{(1R)-1-[N-(1-oxa-4-azaspiro[5.4]decane-4-carbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared following the procedures described in Example 90, substituting 1-oxa-4-azaspiro[5.4]decane, prepared according to the procedure of Bergmann, et al., J. Amer. Chem. Soc. 75 358 (1953), for (±)-*exo*-2-aminonorbornane in Example 90D. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.84 (m, 6H), 1.1-1.7 (m, 11H), 2.2-2.4 (m,2H), 2.54 (s, 3H), 3.34-3.63 (m, 4H), 3.74 (s, 3H), 3.95 (t, 2H, J=6Hz), 4.28 (m, 1H), 5.37 (t, 1H, J=7Hz), 6.98 (br s, 1H), 7.01 (dt, 1H, J=1Hz,8Hz), 7.14 (dt, 1H, J=1Hz,8Hz), 7.30 (dd, 1H, J=1Hz,8Hz), 7.44 (d, 1H, J=8Hz). MS (DCI/NH_3) m/e 580 $(M+H)^+$. Anal calcd for $C_{31}H_{41}N_5O_6 \cdot 0.9$ TFA: C, 57.74; H, 6.19; N, 10.26. Found: C, 57.48; H, 6.63; N, 10.72.

Example 109

2-{(1R)-1-[N-(1-Indolinylcarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared following the procedures described in Example 90, substituting indoline for (±)-*exo*-2-aminonorbornane in Example 90D. The crude material was purified by trituration with hexanes/ether; the resultant material was dissolved in 0.1% aqueous TFA/acetonitrile and lyophilized to give the title compound as a white powder (66 mg). ^{1}H NMR (CD_3OD, 300 MHz) δ 0.88 (d, 6H, J=7Hz), 1.50 (m, 3H), 2.53 (s, 3H), 3.13 (m, 2H), 3.37 (d, 2H, J=6Hz), 3.57 (s, 3H), 3.68 (dt, 1H, J=8Hz,10Hz), 3.82 (dd, 1H, J=8Hz, 10Hz), 4.43 (dd, 1H, J=6Hz,8Hz), 5.43 (t, 1H, J=6Hz), 6.87 (ddd, 1H, J=1Hz,7Hz,8Hz), 6.89 (s, 1H), 6.92 (dt, 1H, J=1Hz,7Hz), 7.03 (dt, 1H, J=1Hz,7Hz), 7.12 (dt, 1H, J=1Hz,7Hz), 7.17 (d, 1H, J=8Hz), 7.23 (d, 1H, J=8Hz), 7.35 (d, 1H, J=8Hz), 7.83 (d, 1H, J=8Hz). MS (DCI/NH_3) m/e 558 $(M+H)^+$, 575 $(M+Na)^+$. Anal calcd for $C_{31}H_{35}N_5O_5 \cdot 1.0$ TFA: C, 59.01; H, 5.40; N, 10.43. Found: C, 59.03; H, 5.72; N, 10.51.

Example 110

2-{(1R)-1-[N-(Decahydroquinolin-1-ylcarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared following the procedures described in Example 90, substituting decahydroquinoline for (±)-*exo*-2-aminonorbornane in Example 90D. ^{1}H NMR (CD_3OD, 300 MHz) of major isomer δ 0.85 (d, 6H, J=7Hz), 1.2-1.9 (m, 15 H), 2.55 (s, 3H), 2.80 (m, 1H), 3.3-3.45 (m, 4H), 3.75 (s, 3H), 3.97 (m, 1H), 4.29 (dd, 1H, J=4Hz,8Hz), (m, 1H), 5.40 (dd, 1H, J= 6Hz,9Hz), 6.96 (s, 1H), 7.01 (dt, 1H, J=1Hz,8Hz), 7.14 (t, 1H, J=7Hz), 7.30 (d, 1H, J=9Hz), 7.42 (dt, 1H, J= 1Hz,8Hz). MS (DCI/NH_3) m/e 578 $(M+H)^+$. Anal calcd for $C_{32}H_{43}N_5O_5 \cdot 0.7$ TFA: C, 61.01; H, 6.70; N, 10.65. Found: C, 61.00; H, 7.01; N, 10.68.

Example 111

2-{(1R)-1-[N-(1,2,3,4-Tetrahydroquinolin-1-ylcarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared following the procedures described in Example 90, substituting 1,2,3,4-tetrahydroquinoline for (±)-*exo*-2-aminonorbornane in Example 90D. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.82 (d, 3H, J=7Hz), 0.84 (d, 3H, J=7Hz), 1.27-1.38 (m, 3H), 1.77-1.89 (m, 2H), 2.55 (s, 3H), 2.67 (t, 1H, J=7Hz), 3.26-3.43 (m, 2H), 3.61 (t, 2H, J=8Hz), 3.71 (s, 3H), 4.36 (dd, 1H, J=6Hz,9Hz), 5.39 (dd, 1H, J=6Hz,7Hz), 6.95 (s, 1H), 6.98-7.22 (m, 6H), 7.28 (d, 1H, J=8Hz), 7.43 (d, 1H, J=8Hz). MS (FAB/NBA) 572 $(M+H)^+$, 594 $(M+Na)^+$. Anal calcd for $C_{32}H_{37}N_5O_5 \cdot 0.9$ TFA: C, 60.21; H, 5.67; N, 10.39. Found: C, 60.29; H, 6.04; N, 10.48.

Example 112

2-{(1R)-1-[N-(N-Cyclohexylaminocarbonyl)-Leucyl-amino]-2-(1-ethyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared following the procedures described in Example 90, substituting Boc-D-(1-ethyl)tryptophan, prepared according to the method of Cook, et al., Chem. Pharm. Bull. 13 88 (1965), but substituting ethyl iodide for methyl iodide, for Boc-D-(1-methyl)-tryptophan in Example 90A. The crude product was triturated with diethyl ether/hexanes, dissolved in acetonitrile and water, and lyophilized to give the product as a white powder. ^{1}H NMR ($CD_3OD/CDCl_3$, 300 MHz) δ 0.82 (d, 3H, J=7Hz), 0.84 (d, 3H, J=7Hz), 1.1-1.9 (m, 13H), 1.40 (t, 3H, J=7Hz), 2.55 (s, 3H), 3.45(m, 1H), 4.14 (q, 2H, J=7Hz), 4.18 (m, 1H), 5.20 (t, 1H, J=7), 6.95 (s, 1H), 7.02 (dt, 1H, J=1Hz,8Hz), 7.15 (dt, 1H, J=1Hz,8Hz), 7.30 (d, 1H, J=8Hz), 7.42 (d, 1H, J=8Hz). MS (DCI/NH_3) m/e 552 $(M+H)^+$, 569 $(M+NH_4)^+$. Anal calcd for $C_{30}H_{41}N_5O_5 \cdot 1.75\ H_2O$: C, 61.78; H, 7.69; N, 12.01. Found: C, 61.58; H, 7.54; N, 11.79.

Example 113

2-{(1R)-1-[N-(N-Cyclohexylaminocarbonyl)-Leucyl-amino]-2-(1-propyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared following the procedures described in Example 90, substituting Boc-D-(1-propyl)tryptophan, prepared according to the method of Cook, et al., Chem. Pharm. Bull., 13: 88 (1965), but substituting propyl iodide for methyl iodide, for Boc-D-(1-methyl)tryptophan in Example 90A. The crude product was triturated with diethyl ether/hexanes, dissolved in acetonitrile and 0.1% aqueous TFA, and lyophilized to give the product as a white powder. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.80 (d, 3H, J=7Hz), 0.82 (d, 3H, J=7Hz), 0.84 (t, 3H, J=8Hz), 1.1-1.7 (m, 13H), 1.80 (m, 2H, J=8Hz), 2.50 (s, 3H), 3.38 (m, 2H), 3.98 (t, 2H, J=8Hz), 4.35 (m, 1H), 5.45 (m, 1H), 6.91 (br s, 1H), 7.05 (d, 1H, J=7Hz), 7.17 (d, 1H, J=7Hz), 7.25 (d, 1H, J=8Hz), 7.50 (d, 1H, J=8Hz). MS (DCI/NH_3) m/e 566 $(M+H)^+$, 583 $(M+NH_4)^+$. Anal calcd for

$C_{31}H_{43}N_5O_5 \cdot 0.4$ TFA,: C, 62.48; H, 7.16; N, 11.46. Found: C, 62.55; H, 7.05; N, 11.47.

Example 114

2-[(1R)-1-[N-(N-Methyl-N-phenylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid

Example 114A

N-(N-Methyl-N-phenylaminocarbonyl)-Leucine

Leucine-O-benzyl ester free base (2.4 g) was dissolved in toluene (25 mL). Triphosgene (1.1 g) was added and the solution heated at reflux for 2.5 hours. The solution was allowed to cool to ambient temperature and the solvent evaporated. The residue was dissolved in $CHCl_3$ (25 mL) and cooled to 0 °C in an ice-bath. N-Methylaniline (1.2 mL) was added and solution stirred cold for 30 minutes. The bath was removed and the solution allowed to stir at ambient temperature for 5 hours. The solution was washed with saturated sodium bicarbonate solution, 1 N H_3PO_4, and brine, dried with $MgSO_4$, and evaporated to give an orange oil which was purified by flash chromatography on silica gel eluting with 20% EtOAc-hexane to give the title compound benzyl ester as a light yellow oil which solidified on standing (3.65 g, 95%). The resultant benzyl ester was dissolved in EtOH (150 mL), the solution was purged of oxygen, 10% Pd/C (150 mg) was added, and the mixture was stirred under hydrogen for two hours. The solvent was removed *in vacuo*, and the residue was taken up in EtOAc and filtered through Celite® to remove the catalyst. The solvent was evaporated *in vacuo* to give the carboxylic acid as a colorless oil (2.62 g, 96%).

Example 114B

2-{(1R)-1-[N-(N-Methyl-N-phenylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid

The crude compound resulting from Example 90C was dissolved in THF (2 mL). HOBt (42 mg), the acid prepared in Example 114A (80 mg) and EDCI (57 mg) were added. N-Methylmorpholine (100 µL) was added and the mixture stirred at room temperature for 18 hours. The solvent was evaporated under reduced pressure and the residue taken up in EtOAc. The solution was washed with saturated $NaHCO_3$ solution, 1 N H_3PO_4 and brine, dried with $MgSO_4$, and evaporated *in vacuo* to give an orange oil which was purified by flash chromatography on silica gel eluting with 50% EtOAc-hexane. This material was dissolved in 30 mL of EtOH, 50 mg of 10% palladium on carbon was added, and the mixture was purged with nitrogen. The nitrogen line was exchanged for a balloon of hydrogen, and the mixture was stirred at ambient temperature for 4 hours. The catalyst was removed by filtration through a pad of Celite®; the solvents were removed *in vacuo*. The crude product was triturated with diethyl ether/hexanes, dissolved in acetonitrile and 0.1% aqueous TFA, and lyophilized to give the product as a pale blue powder (65%). ^1H NMR ($CDCl_3$, 300 MHz) δ 0.75 (d, 3H, J=8Hz), 0.78 (d, 3H, J=8Hz), 1.15-1.4 (m, 3H), 2.55 (s, 3H), 3.22 (s, 3H), 3.42 (m, 2H), 3.71 (s, 3H), 4.38 (m, 1H), 4.70 (d, 1H, J=8Hz), 5.48(dd, 1H, J=6Hz,8Hz), 6.88 (s, 1H), 7.07 (t, 1H, J=7Hz), 7.25 (m, 5H), 7.39 (m, 2H), 7.50 (d, 1H, J=7Hz). MS (FAB) m/e 546 $(M+H)^+$, 568 $(M+Na)^+$, 584 $(M+K)^+$. Anal calcd for $C_{30}H_{35}N_5O_5 \cdot 0.50$ TFA: C, 61.78; H, 5.94; N, 11.62. Found: C, 61.79; H, 6.21; N, 11.60.

Example 115

2-{(1R)-1-[N-(2-Pyridylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared following the procedures described in Example 114, substituting 2-aminopyridine for N-methylaniline in Example 114A. The crude product was triturated with diethyl ether/hexanes, dissolved in acetonitrile and 0.1% aqueous TFA, and lyophilized to give the product as a white powder. MS (FAB) m/e 533 $(M+H)^+$, 555 $(M+Na)^+$, 571$(M+K)^+$. Anal calcd for $C_{28}H_{32}N_6O_5 \cdot 0.70\ H_2O$, 0.80 TFA: C, 55.86; H, 5.42; N, 13.20. Found: C, 55.92; H, 5.64; N, 12.89.

Example 116

2-{(1R)-1-[N-(3-Pyridylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared following the procedures described in Example 114, substituting 3-aminopyridine for N-methylaniline in Example 114A. The crude product was triturated with diethyl ether/hexanes, dissolved in acetonitrile and 0.1% aqueous TFA, and lyophilized to give the product as a white powder. ^1H NMR ($CDCl_3/CD_3OD$, 300 MHz): δ 0.86 (d, 3H, J=5Hz), 0.88 (d, 3H, J=5Hz), 1.42 (m, 2H), 1.53 (m, 1H), 2.55 (s, 3H), 3.39 (m, 2H), 3.70 (s, 3H), 3.71 (m, 1H), 4.33 (m, 1H), 5.44 (m, 1H), 6.91 (s, 1H), 7.02 (t, 1H, J=7Hz), 7.13 (t, 1H, J=7Hz), 7.24 (d, 1H, J=8Hz), 7.46 (d, 1H, J=8Hz), 7.71 (dd, 1H, J=7Hz,8Hz), 8.17 (dd, 1H, J=1Hz,8Hz), 8.26 (d, 1H, J=7Hz), 8.98 (d, 1H, J=1Hz). MS (DCI/NH_3) m/e 533 $(M+H)^+$. Anal calcd for $C_{28}H_{32}N_6O_5 \cdot 2.65$ TFA: C, 47.91; H, 4.18; N, 10.07. Found: C, 47.93; H, 4.62; N, 9.70.

Example 117

2-{(1R)-1-[N-(Pentafluorophenylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared following the procedures described in Example 114, substituting pentafluoroaniline for N-methylaniline in Example 114A. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.83 (d, 3H, J=7Hz), 0.84 (d, 3H, J=7Hz), 1.27-150 (m, 3H), 2.54 (s, 3H), 3.25-3.5 (m, 2H), 3.75 (s, 3H), 4.40 (dd, 1H, J=6Hz,8Hz), 5.39 (dd, 1H, J=6Hz,8Hz), 6.97 (s, 1H), 7.02 (dt, 1H, J=1Hz,8Hz), 7.14 (dt, 1H, J=1Hz,8Hz), 7.30 (d, 1H, J=8Hz), 7.44 (d, 1H, J=8Hz). MS (FAB/NBA) m/e 622 $(M+H)^+$,644 $(M+ Na)^+$. Anal calcd for $C_{29}H_{28}F_5N_5O_5 \cdot 0.8$ TFA: C, 51.49; H, 4.21; N, 9.81. Found: C, 51.68; H, 4.48; N, 9.48.

Example 118

2-{(1R)-1-[N-(2-Hydroxyphenylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared following the procedures described in Example 114, substituting 2-hydroxyaniline for N-methylaniline in Example 114A. The residue was triturated with hexanes/ether; the resultant material was dissolved in 0.1% aqueous TFA/acetonitrile and lyophilized to give the title compound as a white powder (61 mg). ^{1}H NMR (CD_3OD, 300 MHz) δ 0.86 (d, 3H, J=6Hz), 0.88 (d, 3H, J=6Hz), 1.4 (m, 2H), 1.55 (m, 1H), 2.52 (s, 3H), 3.35 (m, 2H), 3.60 (s, 3H), 4.27 (dd, 1H, J=7Hz,8Hz), 5.39 (t, 1H, J=7Hz), 6.7-6.9 (m, 3H), 6.95 (dt, 1H, J=1Hz,7Hz), 6.96 (s, 1H), 7.09 (dt, 1H, J=1Hz,7Hz), 7.26 (d, 1H, J=8Hz), 7.35 (d, 1H, J=8Hz), 7.67 (dd, 1H, J= 1Hz,8Hz). MS (FAB/MeOH) m/e 548 $(M+H)^+$. Anal calcd for $C_{29}H_{33}N_5O_6 \cdot 0.5$ TFA: C, 59.60; H, 5.58; N, 11.58. Found: C, 59.71; H, 5.85; N, 11.61.

Example 119

2-{(1R)-1-[N-(Cyclohexyloxycarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared following the procedures described in Example 114, substituting cyclohexanol for N-methylaniline in Example 114A. The crude final product was purified by trituration with ether/hexanes; the resultant material was dissolved in 0.1% aqueous TFA/acetonitrile and lyophilized to give the title compound as a white powder (60 mg). ^{1}H NMR (CD_3OD, 300 MHz) δ 0.83 (d, 6H, J=7Hz), 1.3-1.9 (m, 13H), 2.54 (s, 3H), 3.3-3.5 (m, 2H), 3.73 (s, 3H), 4.10 (m, 1H), 4.51 (m, 1H), 5.38 (dd, 1H, J=7Hz,8Hz), 6.96 (s, 1H), 7.01 (t, 1H, J=7Hz), 7.13 (dt, 1H, J=1Hz,7Hz), 7.29 (d, 1H, J=8Hz), 7.45 (d, 1H, J=8Hz). MS (FAB/NBA) m/e 539 $(M+H)^+$, 561 $(M+Na)^+$. Anal calcd for $C_{29}H_{38}N_4O_6$ · 0.3 TFA: C, 62.06; H, 6.74; N, 9.78. Found: C, 61.70; H, 6.74; N, 9.98.

Example 120

2-{(1R)-1-[N-(N-Cyclohexyl-N-methylaminocarbonyl)-Cyclohexylalanyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared following the procedures described in Example 90, substituting N-methylcyclohexylamine for (±)-*exo*-2-aminonorbornane and Cha-OBn for Leucyl-OBn · pTsOH in Example 90D. NMR (CD_3OD, 300 MHz) δ 0.75-0.95 (m, 2H), 1.05-1.85 (m, 21H), 2.54 (s, 3H), 2.73 (s, 3H), 3.25-3.40 (m, 2H), 3.74 (s, 3H), 3.90 (m, 1H), 4.35 (t, 1H, J=7Hz), 5.37 (t, 1H, J=7Hz), 6.95 (s, 1H), 6.99 (t, 1H, J=8Hz), 7.14 (dt, 1H, J=1Hz,8Hz), 7.30 (d, 1H, J=8Hz), 7.42 (d, 1H, J=8Hz). MS (DCI/NH_3) m/e 592 $(M+H)^+$. Anal calc for: $C_{33}H_{45}N_5O_5$ · 0.7 TFA: C, 61.53; H, 6.86; N, 10.43. Found: C, 61.47; H, 7.06; N, 10.54.

Example 121

2-{(1R)-1-[N-(N-(Homopiperidin-1-ylcarbonyl)-Leucyl)-N-methylamino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

Example 121A

2-{(1R)-1-(N-Cbz-N-methylamino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid benzyl ester

The title compound was prepared following the procedures described in Examples 90A and 90B, substituting N-Cbz-N-methyl-D-(1-methyl)-tryptophan for Boc-D-(1-methyl)-tryptophan in Example 90A.

Example 121B

2-{(1R)-1-(N-methylamino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

To the compound resulting from Example 121A dissolved in 10 mL of ethanol was added 50 mg of 10% palladium on carbon. The mixture was purged with nitrogen, the nitrogen line was exchanged for a balloon of hydrogen, and the mixture was stirred at ambient temperature for 14 hours. The catalyst was removed by filtration through a pad of Celite®; the solvents were removed *in vacuo* to provide crude product which was used without further purification.

Example 121C

2-{(1R)-1-[N-(N-(Homopiperidin-1-ylcarbonyl)-Leucyl)-N-methylamino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

A solution of 65 mg of the compound resulting from Example 45D, 33 mg of HOBt, 6 drops of N-methylmorpholine, and 45 mg of EDCI in 3 mL THF and 1 mL of DMF was allowed to stir at ambient temperature for 1 hour. The product resulting from Example 121B was added as a solution in 1 mL of DMF, and the reaction mixture was stirred for 14 hours. The resultant solution was concentrated *in vacuo,* and the residue was taken up in EtOAc and washed with 1 N H_3PO_4. The organic phase was concentrated *in vacuo*; and the crude material was

purified by preparative HPLC (Vydac μC18) eluting with a 0-80% gradient of CH_3CN in 0.1% TFA. The desired fractions were lyophilized to give the title compound as a white solid (4 mg). ^1H NMR (CD_3OD, 300 MHz) of major rotamer δ 0.67 (d, 3H, J=6Hz), 0.68 (d, 3H, J=6Hz), 1.45-1.6 (m, 5H), 1.6-1.8 (m, 6H), 2.60 (s, 3H), 2.96 (s, 3H), 3.3-3.5 (m, 6H), 3.75 (s, 3H), 4.57 (dd, 1H, J=4Hz,11Hz), 6.23 (m, 1H), 7.06 (dt, 1H, J=1Hz,7Hz), 7.08 (s, 1H), 7.16 (dt, 1H, J=1Hz,7Hz), 7.31 (d, 1H, J=8Hz), 7.63 (d, 1H, J=8Hz). MS (FAB/MeOH) m/e 552 $(M+H)^+$; 574 $(M+Na)^+$. HRMS calcd for $C_{30}H_{42}N_5O_5$: 552.3186. Found: 552.3176.

Example 122

2-[(1R)-1-[N-(N-Cyclohexylaminocarbonyl-N-methyl-Leucyl)-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid

Example 122A

2-[(1R)-1-[(N-Boc-N-Methyl-Leucyl)-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid benzyl ester

The compound resulting from Example 90C (100 mg) was dissolved in THF (2 mL). HOBt (42 mg), N-Boc-N-methyl-Leu-OH (80 mg, prepared by the method of Cheung and Benoiton, Can. J. Chem. 55 906 (1977), and EDCI (57 mg) were added. N-Methylmorpholine (100 μL) was added and the mixture stirred at room temperature for 18 hours. The solvent was evaporated under reduced pressure and the residue taken up in EtOAc. The solution was washed with saturated $NaHCO_3$ solution, 1 N H_3PO_4 and brine, dried with $MgSO_4$, and evaporated *in vacuo* to give crude product which was used without further purification.

Example 122B

2-{(1R)-1-[N-(N-Cyclohexylaminocarbonyl-N-Methyl-Leucyl)-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid

The compound resulting from Example 122A was dissolved in 30 mL of EtOH, 40 mg of 10% palladium on carbon was added, and the mixture was purged with nitrogen. The nitrogen line was exchanged for a balloon of hydrogen, and the mixture was stirred at ambient temperature for 4 hours. The catalyst was removed by filtration through a pad of Celite®; the solvents were removed *in vacuo*. The crude product was dissolved in 6 mL of trifluoroacetic acid and allowed to stir at ambient temperature for 1 hour. The solvents were removed *in vacuo*; the residue was taken up in toluene and concentrated *in vacuo*. This material was dissolved in 5 mL of DMF; 0.2 mL of N-methylmorpholine was added followed by 5 drops of cyclohexyl isocyanate. The resultant solution was stirred at ambient temperature for 15 hours. The solvents were removed *in vacuo*, and the residue was taken up in EtOAc, washed sequentially with 1 N H_3PO_4 and brine, dried over Na_2SO_4, filtered through Celite®, and concentrated *in vacuo*. The crude product was taken up in ether/hexanes and filtered to afford the title compound as a white solid (122 mg). ^1H NMR (CD_3OD, 300 MHz) δ 0.85 (d, 3H, J=7Hz), 0.87 (d, 3H, J=7Hz), 1.0-19 (m, 13H), 2.50 (s, 3H), 2.66 (s, 3H), 3.3-3.4 (m, 2H), 3.47 (m, 1H), 3.74 (s, 3H), 4.78 (dd, 1H, J=7Hz,9Hz), 5.32 (dd, 1H, J=6Hz,8Hz), 6.99 (s, 1H), 7.00 (dt, 1H, J=1Hz,7Hz), 7.13 (dt, 1H, J=1Hz,7Hz), 7.29 (d, 1H, J=8Hz), 7.42 (d, 1H, J=8Hz). MS (DCI/NH_3) m/e 552 $(M+H)^+$, 569 $(M+NH_4)^+$. Anal calcd for $C_{30}H_{40}N_4O_5 \cdot 0.55$ TFA $\cdot 1.5$ H_2O: C, 58.24; H, 7.00; N, 10.92. Found: C, 58.35; H, 7.31; N, 10.58.

Example 123

2-[(1R)-1-[(2R)-2-(3-Cyclohexyl-2-imidazolidone-1-yl)-4-methylvaleramido]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid

Example 123A

N-Benzyloxycarbonyl-N-cyclohexyl-glycine methyl ester

Cyclohexanone (3.0 g) was dissolved in methanol (25 mL). Glycine methyl ester hydrochloride (3.8 g) was added and the mixture adjusted to pH 5.5 by addition of acetic acid. Sodium cyanoborohydride (1.9 g) was added and the solution stirred at ambient temperature for 24 hours. The solvents were evaporated and the residue dissolved in EtOAc (50 mL). The resulting solution was washed with water (25 mL), saturated sodium bicarbonate solution (2 x 25 mL), and brine (25 mL), dried with Na_2SO_4 and evaporated to give a yellow oil which was purified by flash chromatography on silica gel eluting with 70% EtOAc-hexane to give 1.85 g of colorless oil (35%).

The resultant N-cyclohexyl-glycine methyl ester (1.8 g) and sodium bicarbonate (0.9 g) were suspended in dimethylformamide (25 mL). The suspension was cooled to 0 °C in an ice bath and benzyl chloroformate (1.5 mL) was added. The mixture was stirred at 0 °C for 3 hours and then allowed to warm to room temperature. Water (75 mL) was added and the mixture extracted with EtOAc (2 x 50 mL). The organic extracts were combined, washed with saturated sodium bicarbonate solution (2 x 25 mL), 1 N H_3PO_4 (25 mL), and brine (25 mL). The organic layer was dried with Na_2SO_4 and evaporated to give a yellow oil which was purified by flash chromatography on silica gel eluting with 20% EtOAc-hexane to give 1.65 g (52%) of the title compound as a colorless oil.

Example 123B

N-(2-(N-Cbz-N-cyclohexylamino)ethyl)-Leucine tert-butyl ester

The compound resulting from Example 123A (1.63 g) was dissolved in THF (5 mL). LiOH (0.5 g) in water (2 mL) was added, and the mixture was stirred at ambient temperature for 18 hours. The mixture was made acidic by the addition of 1 N H_3PO_4 and extracted with EtOAc (2 x 50 mL). The organic extracts were combined, dried with Na_2SO_4, and evaporated to give a pale yellow oil (1.35 g, 87%).

The resulting substituted glycine carboxylic acid was dissolved in THF (25 mL). Leucine tert-butyl ester hydrochloride (1.0 g), HOBt (0.65 g), EDCI (0.9 g), and N-methylmorpholine (1.2 mL) were added. DMF (15 mL) was added to the mixture and the solution stirred at ambient temperature for 18 hours. Water (75 mL) was added and the mixture extracted with EtOAc (2 x 50 mL). The organic extracts were combined, washed with saturated sodium bicarbonate solution (2 x 25 mL), 1 N H_3PO_4 (25 mL), and brine (25 mL). The organic layer was dried with Na_2SO_4 and evaporated to give a yellow oil which was purified by flash chromatography on silica gel eluting with 25% EtOAc-hexane to give 1.4 g (67%) of the coupled product as a white solid.

The product (1.35 g) was dissolved in THF (20 mL) and the solution cooled to 0 °C. Borane in THF (1 N, 25 mL) was added slowly and the solution stirred at 0 °C for five hours. 10% HOAc in MeOH (20 mL) was added very slowly to the cooled reaction mixture. After the addition was complete, the reaction was allowed to warm to ambient temperature and stirred for 18 hours. The solution was made basic with saturated sodium bicarbonate solution and extracted with EtOAc (3 x 35 mL). The organic layers were combined, dried with Na_2SO_4, and evaporated to give a yellow oil which was purified by flash chromatography on silica gel eluting with 25% EtOAc-hexane to give 0.5 g (38%) of the title compound as a colorless oil.

Example 123C

(2R)-2-[-(3-Cyclohexyl-2-imidazolidone-1-yl)]-4-methylvaleric acid

The compound resulting from Example 123B (0.45 g) was dissolved in ethanol (15 mL). 10% Palladium on carbon (50 mg) was added. The flask was fitted with a three-way stopcock connected to a hydrogen–filled balloon and a nitrogen/vacuum manifold. The flask was evacuated, filled with nitrogen, evacuated again, and then put under a hydrogen atmosphere. The mixture was stirred at ambient temperature for 5 hours. The hydrogen was evacuated and the flask filled with nitrogen. The catalyst was removed by filtration through a pad of Celite® and the solvent removed *in vacuo* to give the de-protected compound as a yellow oil (0.28 g, 80% yield).

The resultant diamine (0.28 g) was dissolved in $CHCl_3$ (15 mL) and carbonyldiimidazole (0.15 g) was added. The solution was heated at reflux for six hours, allowed to cool to ambient temperature, and evaporated. The residue was dissolved in EtOAc (25 mL), washed with saturated sodium bicarbonate solution (2 x 25 mL), 1 N H_3PO_4 (25 mL), and brine (25 mL). The organic layer was dried with Na_2SO_4 and evaporated to give a yellow oil (0.29 g, 95% yield).

The tert-butyl ester (0.29 g) was dissolved in 4 N HCl in dioxane (5 mL) and stirred at ambient temperature for 18 hours. The solvent was evaporated to give a white solid which was dissolved in acetone (10 mL) and evaporated. The white solid was triturated with diethyl ether/hexane and collected by filtration to give 0.17 g (70%) of the title compound as a white soild.

Example 123D

2-{(1R)-1-[(2R)-2-(3-Cyclohexyl-2-imidazolidone-1-yl)-4-methylvaleramido]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The crude compound resulting from Example 90C (220 mg) was dissolved in THF (4 mL). HOBt (80 mg), the acid prepared in Example 123C (125 mg) and EDCI (115 mg) were added. N-Methylmorpholine (200 µL) was added and the mixture stirred at room temperature for 18 hours. The solvent was evaporated under reduced pressure and the residue taken up in EtOAc. The solution was washed with saturated $NaHCO_3$ solution, 1 N H_3PO_4 and brine, dried with $MgSO_4$, and evaporated *in vacuo* to give an orange oil which was purified by flash chromatography on silica gel eluting with 50% EtOAc-hexane. This material was dissolved in 30 mL of EtOH, 50 mg of 10% palladium on carbon was added, and the mixture was purged with nitrogen. The nitrogen line was exchanged for a balloon of hydrogen, and the mixture was stirred at ambient temperature for 4 hours. The catalyst was removed by filtration through a pad of Celite®; the solvents were removed *in vacuo*. The resultant material was dissolved in acetonitrile and water and lyophilized to give the product as a white powder (120 mg, 47%). ^1H NMR ($CDCl_3$-CD_3OD, 300 MHz) δ 0.85 (d, 6H, J=7Hz), 1.25-1.9 (m, 13H), 2.53 (s, 3H), 3.34 (m, 4H), 3.58 (m, 2H), 3.75 (m, 1H), 3.77 (s, 3H), 4.36 (t, 1H, J=7Hz), 5.38 (t, 1H, J=7Hz), 6.94 (s, 1H), 7.05 (t, 1H, J=7Hz), 7.18 (t, 1H, J=7Hz), 7.29 (d, 1H, J=8Hz), 7.46 (d, 1H, J=8Hz). MS (DCI/NH_3) m/e 564 $(M+H)^+$, 581 $(M+NH_4)^+$. Anal calcd for $C_{31}H_{41}N_5O_5 \cdot 1.3\ H_2O$: C, 63.61; H, 7.47; N, 11.96. Found: C, 63.57; H, 7.29; N, 11.99.

Example 124
2-{(1R)-1-[N-(1-Methylcyclohexylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

Example 124A.
N-(1-Methylcyclohexylaminocarbonyl)-Leucyl-OH

To a solution of 1.06 g (7.5 mmol) of 1-methylcyclohexane-1-carboxylic acid in 40 mL of toluene were added 1.61 mL of diphenylphosphorylazide (2.06 g, 1 eq) and 1.65 mL (1.52 g, 15 mmol) of N-methylmorpholine. The resultant mixture was heated at 70 °C for 2 hours, cooled to room temperature, and added dropwise to a solution of 1.97 g (5 mmol) of Leu-OBn·TsOH and 1.1 mL of N-methylmorpholine in 20 mL of toluene. The reaction mixture was stirred overnight at ambient temperature and then washed with sodium bicarbonate solution, 1 N H_3PO_4, and brine, and concentrated *in vacuo*. The crude product (2.5 g) was dissolved in 50 mL of EtOH, 50 mg of 10% palladium on carbon was added, and the mixture was purged with nitrogen. The nitrogen line was exchanged for a balloon of hydrogen, and the mixture was stirred at ambient temperature for 4 hours. The catalyst was removed by filtration through a pad of Celite®, and the solvents were removed *in vacuo* to give the title compound which was used without further purification.

Example 124B
2-{(1R)-1-[N-(1-Methylcyclohexylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared following the procedures described in Example 123D, substituting the compound of Example 124A for the compound of Example 123C. ^1H NMR (CD_3OD, 300 MHz) δ 0.83 (d, 3H, J=6Hz), 0.84 (d, 3H, H=6Hz), 1.25 (s, 3H) 1.26-1.56 (m, 11H), 1.8-1.9 (m, 2H), 2.57 (s, 3H), 3.2-3.5 (m, 2H), 3.74 (s, 3H), 4.14 (dd, 1H, J=6Hz,9Hz), 5.36 (dd, 1H, J= 6Hz,7Hz), 6.97 (s, 1H), 7.05 (dt, 1H, J= 1Hz,8Hz), 7.13 (dt, 1H, J=1Hz,8Hz), 7.29 (d, 1H, J=8Hz), 7.45 (d, 1H, J=8Hz). MS (DCI/NH_3) m/e 552 $(M+H)^+$, 569 $(M+NH_4)^+$. Anal calcd

for $C_{30}H_{41}N_5O_5 \cdot 0.8$ TFA: C, 59.04; H, 6.55; N, 10.89. Found: C, 59.27; H, 6.79; N, 10.98.

Example 125

2-{(1R)-1-[N-(Phenylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid

Example 125A

N-(Phenylaminocarbonyl)-Leucyl-OH

Leu-OBn · pTsOH (2.0 g) was suspended in THF (10 mL). N-Methylmorpholine (0.56 mL) and phenylisocyanate (0.55 mL) were added and the solution stirred at ambient temperature for four hours. The solvent was evaporated and the residue taken up in EtOAc (50 mL) and washed with saturated sodium bicarbonate solution, 1 N H_3PO_4, and brine. The organic layer was dried with $MgSO_4$ and evaporated to give a colorless oil which was purified by flash chromatography on silica gel eluting with 20% EtOAc-hexanes. The resulting colorless oil was taken up in EtOH (25 mL). 10% Palladium on carbon (0.5 g) was added. The flask was fitted with a three-way stopcock connected to a hydrogen-filled balloon and a nitrogen/vacuum manifold. The flask was evacuated, filled with nitrogen, evacuated again, and then put under a hydrogen atmosphere. The reaction was stirred at ambient temperture for 20 hours. The hydrogen was evacuated and the flask filled with nitrogen. The catalyst was removed by filtration through Celite® and the solvent evaporated to give the title compound as a pale yellow oil (1.08 g, 85%).

Example 125B

2-{(1R)-1-[N-(Phenylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid

The crude compound resulting from Example 90C (140 mg) was dissolved in THF (4 mL). HOBt (50 mg), the acid prepared in Example 125A (100 mg) and EDCI (65 mg) were added. N-Methylmorpholine (150 µL) was added and the mixture stirred at room temperature for 18 hours. The solvent was evaporated under reduced pressure and the residue taken up in EtOAc. The solution was washed with saturated $NaHCO_3$ solution, 1 N H_3PO_4 and brine, dried with $MgSO_4$, and evaporated *in vacuo* to give a yellowish oil which was purified by flash chromatography on silica gel eluting with 50% EtOAc-hexane. This material was dissolved in 30 mL of EtOH; 50 mg of 10% palladium on carbon was added, and the mixture was purged with nitrogen. The nitrogen line was exchanged for a balloon of hydrogen, and the mixture was stirred at ambient temperature for 4 hours. The catalyst was removed by filtration through a pad of Celite®, and the solvents were removed *in vacuo*. The crude product was triturated with diethyl ether/hexanes, dissolved in acetonitrile and 0.1% aqueous TFA, and lyophilized to give the product as a white powder (118 mg, 55%). ^1H NMR (CD_3OD-$CDCl_3$, 300 MHz) δ 0.85 (d, 3H, J=8Hz), 0.88 (d, 3H, J=8Hz), 1.35-1.6 (m, 3H), 2.52 (s, 3H), 3.38 (d, 2H, J=10Hz), 3.56 (s,3H), 4.32 (dd, 1H, J=6Hz,10Hz), 5.43(t, 1H, J=6Hz), 6.90 (s, 1H), 6.98 (m, 2H), 7.11 (dt, 1H, J=1Hz,7Hz), 7.25 (m, 3H), 7.34 (m, 3H). MS (DCI/NH_3) m/e 532 $(M+H)^+$, 549 $(M+NH_4)^+$. Anal calcd for $C_{29}H_{33}N_5O_5$ · 0.33 TFA: C, 62.58; H, 5.90; N, 12.30. Found: C, 62.65; H, 5.84; N, 12.20.

Example 126

2-[(1R)-1-[N-(3-Fluorophenylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared according to the procedures described in Example 125 but substituting 3-fluorophenyl isocyanate for phenyl isocyanate in Example 125A. The crude product was triturated with diethyl ether/hexanes, dissolved in acetonitrile and 0.1% aqueous TFA, and lyophilized to give the product as a white powder. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.78 (d, 3H, J=6Hz), 0.82 (d, 2H, J=6Hz), 1.2-1.35 (m, 2H), 1.45-1.55 (m, 1H), 2.42 (s, 3H), 3.32 (m, 2H), 3.48 (s, 3H), 4.36 (m, 1H), 5.42 (dd, 1H, J=7Hz,8Hz), 5.96 (m, 1H), 6.59 (dt, 1H, J=1Hz,7Hz), 6.80 (m, 2H), 6.95 (m, 2H), 7.03 (m, 1H), 7.12 (m, 2H), 7.25 (m, 2H). MS (FAB) m/e 546 $(M+H)^+$, 568 $(M+Na)^+$, 584 $(M+K)^+$. Anal calcd for $C_{29}H_{32}N_5O_5F \cdot 1.50$ TFA: C, 55.23; H, 4.91; N, 10.29. Found: C, 55.31; H, 5.29; N, 9.88.

Example 127

2-[(1R)-1-[N-(N,N-Diphenylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared according to the procedures described in Example 125 but substituting diphenylcarbamyl chloride for phenyl isocyanate in Example 125A. The crude product was triturated with diethyl ether/hexanes, dissolved in acetonitrile and 0.1% aqueous TFA, and lyophilized to give the product as a white powder. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.78 (d, 3H, J=7Hz), 0.84 (d, 2H, J=7Hz), 1.28 (m, 2H), 1.37 (m, 1H), 2.55 (s, 3H), 3.38 (m, 2H), 3.70 (s, 3H), 4.38 (m, 1H), 5.39 (dd, 1H, J=7Hz,8Hz), 6.95 (s, 1H), 7.02 (dt, 1H, J=1Hz,7Hz), 7.10 (m, 3H), 7.21 (m, 3H), 7.30 (m, 4H), 7.38 (m, 2H), 7.45 (d, 1H, J=7Hz). MS (DCI/NH_3) m/e 608 $(M+H)^+$, 625 $(M+NH_4)^+$. Anal calcd for $C_{35}H_{37}N_5O_5 \cdot 0.30$ TFA: C, 66.61; H, 5.86; N, 10.91. Found: C, 66.78; H, 6.43; N, 10.35.

Example 128

2-{(1R)-1-[N-(2-Fluorophenylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared according to the procedures described in Example 125 but substituting 2-fluorophenyl isocyanate for phenyl isocyanate in Example 125A. The crude product was triturated with diethyl ether/hexanes, dissolved in acetonitrile and 0.1% aqueous TFA, and lyophilized to give the product as a white powder. ^{1}H NMR (CD_3OD, 300 MHz): δ 0.81 (d, 3H, J=4Hz), 0.83 (d, 2H, J=4Hz), 1.35 (m, 2H), 1.5 (m, 1H), 2.52 (s, 3H), 3.38 (m, 2H), 3.65 (s, 3H), 4.28 (m, 1H), 5.40 (dd, 1H, J=7Hz,8Hz), 6.95 (m, 3H), 7.08 (m, 4H), 7.25 (d, 1H, J=7Hz), 7.42 (d, 1H, J=7Hz). MS (DCI/NH_3) m/e 550 $(M+H)^+$, 567 $(M+NH_4)^+$. Anal calcd for $C_{29}H_{32}N_5O_5F \cdot 0.35$ TFA: C, 60.51; H, 5.53; N, 11.88. Found: C, 60.61; H, 5.57; N, 11.74.

Example 129

2-{(1R)-1-[N-(4-Fluorophenylaminocarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared according to the procedures described in Example 125 but substituting 4-fluorophenyl isocyanate for phenyl isocyanate in Example 125A. The crude product was triturated with diethyl ether/hexanes, dissolved in acetonitrile and water, and lyophilized to give the product as a white powder. ^{1}H NMR ($CDCl_3$-CD_3OD, 300 MHz) δ 0.82 (d, 3H, J=4Hz), 0.86 (d, 2H, J=4Hz), 1.35 (m, 2H), 1.5 (m, 1H), 2.55 (s, 3H), 3.38 (m, 2H), 3.63 (s, 3H), 4.28 (m, 1H), 5.40 (m, 1H), 6.95 (m, 4H), 7.10 (m, 1H), 7.32 (m, 3H), 7.40 (m, 1H). MS (FAB) m/e 550 $(M+H)^+$, 572 $(M+Na)^+$. Anal calcd for $C_{29}H_{32}N_5O_5F \cdot 2.0$ H_2O: C, 59.48; H, 6.20; N, 11.96. Found: C, 59.11; H, 6.00; N, 11.36.

Example 130

2-[(1R)-1-[N-(N-Carbazolylcarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid

The title compound was prepared according to the procedures described in Example 125 but substituting carbazole-N-carbonyl chloride for phenyl isocyanate in Example 125A. The crude product was purified by preparative HPLC (Vydac μC18) eluting with a 10-70% gradient of CH_3CN in 0.1% TFA. The appropriate fraction was lyophilized to give the product as a white solid. ^1H NMR (CD_3OD, 300 MHz) δ 0.78 (d, 3H, J=7Hz), 0.84 (d, 2H, J=7Hz), 1.28 (m, 2H), 1.37 (m, 1H), 2.75 (s, 3H), 3.42 (m, 2H), 3.60 (s, 3H), 4.42 (m, 1H), 5.43 (dd, 1H, J=7Hz,8Hz), 6.95 (s, 1H), 7.02 (dt, 1H, J=1Hz,7Hz), 7.10 (m, 3H), 7.21 (m, 3H), 7.30 (m, 4H), 7.35 (dt, 2H, J=1Hz,8Hz), 7.38 (m, 2H), 7.45 (d, 1H, J=7Hz), 7.47 (t, 2H, J=8Hz), 8.04 (dt, 2H, J=1Hz,8Hz), 8.10 (d, 2H, J=8Hz). MS (DCI/NH_3) m/e 606 $(M+H)^+$, 623 $(M+NH_4)^+$. Anal calcd for $C_{35}H_{35}N_5O_5 \cdot 1.0$ TFA: C, 60.89; H, 6.35; N, 9.60. Found: C, 60.78; H, 6.41; N, 9.35.

Example 131

2-[(1R)-1-[N-(7-Azaindolin-1-ylcarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid

Example 131A

N-(7-Azaindole-1-carbonyl)-Leucine benzyl ester

To a solution of 7-azaindole (2.36 g, 20 mmol) in 100 mL of 3:1 THF/DMF, stirring at 0 °C, 0.60 g of sodium hydride (1 eq) was added in four portions. The resultant solution was stirred for 15 minutes and then a solution of 4.03 g (1 eq) of p-nitrophenylchloroformate in 10 mL of THF was added rapidly. The reaction mixture was warmed slowly to ambient temperature over 3 hours. The solvents were removed *in vacuo*; the residue was taken up in EtOAc and washed sequentially with sodium bicarbonate solution and brine. The crude product was added at 0 °C to a solution of 1.97 g (5.0 mmol) of Leucine benzyl ester · p-tosylate and 2

mL of N-methylmorpholine in 15 mL of THF. The resultant solution was warmed to ambient temperature overnight. The solvents were removed *in vacuo*; the residue was taken up in EtOAc and washed sequentially with 1 N NaOH (3x), water, and brine. The crude product was purified by flash chromatography on silica gel eluting with 3:1 going to 2:1 hexanes-ether to give 1.38 g (76%) of the title compound.

Example 131B

N-(7-Azaindole-1-carbonyl)-Leucyl-OH

and

N-(7-Azaindoline-1-carbonyl)-Leucyl-OH

The compound resulting from Example 97A (400 mg) was dissolved in 20 mL of ethanol, 50 mg of 10% palladium on carbon was added, and the mixture was purged with nitrogen. The nitrogen line was exchanged for a balloon of hydrogen, and the mixture was stirred at ambient temperature for 4.5 hours. The catalyst was removed by filtration through a pad of Celite®, and the solvents were removed *in vacuo* to give a ~1:1 mixture of the title compounds, which was carried forward without further purification or separation.

Example 131C

2-[(1R)-1-[N-(7-Azaindolin-1-ylcarbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid

The compound resulting from Example 90C (170 mg) was dissolved in THF (5 mL) and DMF (2 mL). HOBt (60 mg), the mixture of acids prepared in Example 131B (110 mg) and EDCI (90 mg) were added. N-Methylmorpholine (150 µL) was added and the mixture stirred at room temperature for 18 hours. The solvent was evaporated under reduced pressure and the residue taken up in EtOAc. The solution was washed with saturated $NaHCO_3$ solution, 1 N H_3PO_4 and brine, dried with $MgSO_4$, and evaporated *in vacuo*. After extractive workup, the products were separated by flash chromatography on silica gel, eluting with 1:1 going to 1:2 hexanes-EtOAc. The less mobile

product was dissolved in 20 mL of ethanol, 50 mg of 10% palladium on carbon was added, and the mixture was purged with nitrogen. The nitrogen line was exchanged for a balloon of hydrogen, and the mixture was stirred at ambient temperature for 4 hours. The catalyst was removed by filtration through a pad of Celite®, and the solvents were removed *in vacuo*. The resultant material was dissolved in 0.1% aqueous TFA in acetonitrile and lyophilized to give a white powder (96 mg). ^{1}H NMR (CD_3OD, 300 MHz) δ 0.86 (d, 6H, J=6Hz), 1.3-1.6 (m, 3H), 2.54 (s, 3H), 3.14 (m, 2H), 3.35 (m, 2H), 3.58 (s, 3H), 3.97 (t, 2H, J=9Hz), 4.40 (dd, 1H, J=5Hz,9Hz), 5.39 (dd, 1H, J=7Hz,8Hz), 6.9-7.0 (m, 3H), 7.08 (dt, 1H, J=1Hz,7Hz), 7.27 (d, 1H, J=8Hz), 7.47 (d, 1H, J=8Hz), 7.66 (m, 1H), 7.95 (dd, 1H, J=1Hz,6Hz). MS (FAB/NBA) m/e 559 $(M+H)^+$, 581 $(M+Na)^+$. Anal calcd for $C_{30}H_{34}N_6O_5 \cdot 1.5$ TFA: C, 54.32; H, 4.90; N, 11.52. Found: C, 54.59; H, 4.69; N, 11.42.

Example 132

2-{(1R)-1-[N-(7-Azaindole-1-carbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid

Cyclohexadiene (0.1 mL) was added to a suspension of 110 mg of 10% Pd/C in 2 mL of MeOH. The mixture was stirred for 10 minutes, and then a solution of the more mobile product from Example 131C in 4 mL of 1:1 MeOH-EtOAc was added. The resultant suspension was stirred for 4 hours at ambient temperature. The catalyst was removed by filtration through a pad of Celite®, and the solvents were removed *in vacuo*. The resultant material was dissolved in 0.1% aqueous TFA in acetonitrile and lyophilized to give the title compound as a white powder (35 mg). ^{1}H NMR (CD_3OD, 300 MHz) δ 0.84 (d, 3H, J=6Hz), 0.87 (d, 3H, J=6Hz), 1.4-1.6 (m, 3H), 2.53 (s, 3H), 3.38 (m, 2H), 3.68 (s, 3H), 4.55 (m, 1H), 5.43 (dd, 1H, J=6Hz,8Hz), 6.66 (d, 1H, J=4Hz), 6.96 (m, 2H), 7.08 (dt, 1H, J=1Hz,7Hz), 7.27 (m, 2H), 7.48 (d, 1H, J=8Hz), 7.88 (d, 1H, J=4Hz), 8.06 (dd, 1H, J=1Hz,8Hz), 8.31 (dd, 1H, J=1Hz,5Hz). MS (DCI/NH_3) m/e 557 $(M+H)^+$, 574 $(M+NH_4)^+$. Anal calcd for $C_{30}H_{32}N_6O_5$

· 0.6 TFA: C, 59.96; H, 5.26; N, 13.45. Found: C, 60.34; H, 5.61; N, 13.21.

Example 133

2-((1R)-1-[N-(Indole-1-carbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid

Example 133A

N-(Indole-1-carbonyl)-Leucyl-OH

Indole-1-carboxylic acid (0.64 g, 4.0 mmol, prepared according to the procedure of Boger and Patel, J. Org. Chem. 152 3934 (1987), was dissolved in 20 mL of dichloromethane, EDCI (0.58 g, 3 mmol) was added, and the solution was stirred at ambient temperature for 30 minutes. Leu-OBn (0.55 g, 2.5 mmol) was added, and the solution was stirred for 16 hours at ambient temperature. The solvents were removed *in vacuo*, and the residue was taken up in EtOAc, washed with water, sodium bicarbonate solution, 1 N H_3PO_4, and brine, and concentrated *in vacuo*. The product was purified by flash chromatography on silica gel.

A sample of this material (170 mg, 0.49 mmol) was added to a suspension of 87 mg of 10% Pd/C in 1.5 mL of MeOH, the mixture was purged with nitrogen, and 0.1 mL of cyclohexadiene was added. The resultant suspension was stirred at ambient temperature for 1 hour. The catalyst was removed by filtration through a pad of Celite®, and the solvents were removed *in vacuo* to give a product which was used without further purification.

Example 133B

2-[(1R)-1-[N-(Indole-1-carbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid

The compound resulting from Example 90C (95 mg) was dissolved in THF (4 mL) and DMF (2 mL). HOBt (42 mg), the compound of Example 133A (90 mg) and EDCI (57 mg) were added. N-Methylmorpholine (200 µL) was added and the mixture stirred at room temperature for 18 hours. The solvent was evaporated under reduced pressure and the residue taken up in EtOAc. The solution was washed with saturated $NaHCO_3$ solution, 1 N H_3PO_4 and brine, dried with $MgSO_4$, and evaporated *in vacuo*. The product was purified by flash chromatography on silica gel, eluting with 4:1 going to 5:2 hexanes-EtOAc. The resultant product was added to a suspension of 36 mg of 10% Pd/C in 1 mL of MeOH, the mixture was purged with nitrogen, and 0.1 mL of cyclohexadiene was added. The resultant suspension was stirred at ambient temperature for 2 hours. The catalyst was removed by filtration through a pad of Celite®; the solvents were removed *in vacuo*. The crude product was triturated with diethyl ether/hexanes, dissolved in acetonitrile and 0.1% aqueous TFA, and lyophilized to give the product as a white powder. ^1H NMR (CD_3OD, 300 MHz) δ 0.89 (d, 3H, J=7Hz), 0.90 (d, 3H, J=7Hz), 1.4-1.7 (m, 3H), 2.50 (s, 3H), 3.3-3.4 (m, 2H), 3.53 (s, 3H), 4.52 (dd, 1H, J=6Hz,10Hz), 5.43 (dd, 1H, J=7Hz,8Hz), 6.62 (d, 1H, J=4Hz), 6.89-6.96 (m, 2H), 7.06 (dt, 1H, J=1Hz,8Hz), 7.14-7.30 (m, 3H), 7.36 (d, 1H, J=7Hz), 7.57 (dd, 1H, J=1Hz,7Hz), 7.65 (d, 1H, J=4Hz), 8.16 (dd, 1H, J=1Hz,7Hz). MS (DCI/NH_3) 556 $(M+H)^+$, 573 $(M+NH_4)^+$. Anal calcd for $C_{31}H_{33}N_5O_5 \cdot 0.9$ TFA: C, 59.85; H, 5.19; N, 10.64. Found: C, 60.15; H, 5.46; N, 10.49.

Example 134
2-[(1R)-1-[N-(Indole-3-carbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid

Example 134A
N-(Indole-3-carbonyl)-Leu-OH

Indole-3-carboxylic acid (0.39 g, 2.4 mmol) was combined with Leu-OBn (0.53 g, 2.0 mmol) in 5 mL of THF and 2 mL of DMF. HOBt (0.32 g) and EDCI (0.37g, 2.4 mmol) were added, followed by 0.3 mL of N-methylmorpholine, and the solution was stirred for 16 hours at ambient temperature. The solvents were removed *in vacuo*, and the residue was taken up in EtOAc and washed with water, sodium bicarbonate solution, 1 N H_3PO_4, and brine, and concentrated *in vacuo*. The product was purified by flash chromatography on silica gel.

The benzyl ester was dissolved in 50 mL of ethanol, 100 mg of 10% palladium on carbon was added, and the mixture was purged with nitrogen. The nitrogen line was exchanged for a balloon of hydrogen, and the mixture was stirred at ambient temperature for 4 hours. The catalyst was removed by filtration through a pad of Celite®, and the solvents were removed *in vacuo* to give the title compound as a colorless oil.

Example 134B
2-[(1R)-1-[N-(Indole-3-carbonyl)-Leucyl-amino]-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-oxazole-4-carboxylic acid

The crude compound resulting from Example 90C (140 mg) was dissolved in THF (4 mL). HOBt (50 mg), the acid resulting from Example 134A (100 mg) and EDCI (65 mg) were added. N-Methylmorpholine (150 µL) was added and the mixture stirred at room temperature for 18 hours. The solvent was evaporated under reduced pressure and the residue taken up in EtOAc. The solution was washed with saturated $NaHCO_3$ solution, 1 N H_3PO_4 and brine, dried with $MgSO_4$, and

evaporated *in vacuo* to give a yellowish oil which was purified by flash chromatography on silica gel eluting with 50% EtOAc-hexane.

The benzyl ester was dissolved in 30 mL of EtOH, 50 mg of 10% palladium on carbon was added, and the mixture was purged with nitrogen. The nitrogen line was exchanged for a balloon of hydrogen, and the mixture was stirred at ambient temperature for 4 hours. The catalyst was removed by filtration through a pad of Celite®, and the solvents were removed *in vacuo*. The crude product was triturated with diethyl ether/hexanes, dissolved in acetonitrile and 0.1% aqueous TFA, and lyophilized to give the product as a white powder. ^{1}H NMR (CD_3OD, 300 MHz) δ 0.90 (d, 6H, J=6Hz), 1.5-1.7 (m, 3H), 2.50 (s, 3H), 3.28 (s, 3H), 3.3-3.45 (m, 2H), 4.67 (dd, 1H, J=6Hz,9Hz), 5.43 (t, 1H, J = 6Hz), 6.84 (s, 1H), 6.89 (dt, 1H, J=1Hz,8Hz), 7.04 (dt, 1H, J=1Hz,8Hz), 7.13-7.27 (m, 4H), 7.45 (dd, 1H, J=1Hz,8Hz), 7.90 (s, 1H), 8.19 (dd, 1H, J=1Hz,7Hz). MS (FAB/NBA) m/e 556 $(m+H)^+$, 578 $(M+Na)^+$. Anal calcd for $C_{31}H_{33}N_5O_5 \cdot 1.2$ TFA: C, 57.94; H, 4.98; N, 10.11. Found: C, 58.05; H, 4.94; N, 10.24.

As an indication that the compounds described herein act through binding to endothelin receptors, the compounds have been evaluated for their ability to bind to the endothelin receptor.

Binding Assay

ET_A Receptor

Preparation of membranes from MMQ cells:

MMQ [MacLeod/MacQueen/Login cell line (prolactin secreting rat pituitary cells which are known to contain ET_A receptors)] cells from 150 ml culture flasks were collected by centrifugation (1000xg for 10 min) and then homogenized in 25 ml of 10 mM Hepes (pH 7.4) containing 0.25 M sucrose and protease inhibitors [3 mM EDTA , 0.1 mM PMSF, and 5 µg/ml Pepstatin A] by a micro ultrasonic cell disruptor (Kontes).

The mixture was centrifuged at 1000xg for 10 min. The supernatant was collected and centrifuged at 60,000xg for 60 min. The precipitate was resuspended in 20 mM Tris, pH 7.4 containing the above protease inhibitors and centrifuged again. The final pellet was resuspended in 20 mM Tris, pH 7.4 containing protease inhibitors and stored at -80 °C until used. Protein content was determined by the Bio-Rad dye-binding protein assay.

[^{125}I]ET-1 binding to membranes:

Binding assays were performed in 96-well microtiter plates pretreated with 0.1% BSA. Membranes prepared from cells were diluted ~100 fold in Buffer B (20 mM Tris, 100 mM NaCl, 10 mM $MgCl_2$, pH 7.4, with 0.2% BSA, 0.1 mM PMSF, 5 µg/ml Pepstatin A, 0.025% bacitracin, and 3 mM EDTA) to a final concentration of 0.2 mg/mL of protein. In competition studies, membranes (0.02 mg) were incubated with 0.1 nM of [^{125}I]ET-1 in Buffer B (final volume: 0.2 mL) in the presence of increasing concentrations of unlabeled ET-1, BQ123, or FR139317 (reference compounds) or other tested compounds for 4 hours at 25 °C. After incubation, unbound ligands were separated from bound ligands by a vacuum filtration method using glass-fiber filter strips in PHD cell harvesters (Cambridge Technology, Inc., MA), followed by washing the filter strips with saline (1 mL) for three times. Nonspecific binding was determined in the presence of 1 µM ET-1. The data are shown in Table 1. The per cent inhibition at a concentration of 1 µM is shown. The data show that the compounds of the invention bind to the endothelin receptor.

Table 1
Binding Data

Ex. No.	% Inhibition at 1 μM	Ex. No.	% Inhibition at 1 μM
1F	73.0	43B	95.8
2	69.8	44	94.6
5	42.0	49	17.0
6	36.0	50	14.0
7	47.0	54C	18.0
8	19.0	55	30.0
10	45.6	56	14.0
13	92.0	57E	59.0
17B	53.4	58	71.9
18	44.8	61	14.0
21	39.9	63	54.0
22	27.6	64	21.0
24	30.6	65	23.0
27F	97.9	66	25.0
28	94.8	69	31.2
29	93.7	70	26.4
30	88.4	71	34.5
31	87.6	74	43.4
32	89.0	75B	57.7
33	86.4	76B	66.8
34	93.9	79	21.5
35	89.7	80	15.2
36	86.7	81	18.5
37	59.3	82	34.5
42B	88.3	83	33.1

Ex. No.	% Inhibition at 1 μM	Ex. No.	% Inhibition at 1 μM
84	46.9	109	93.0
85	97.5	110	94.4
86	21.7	111	94.0
87D	13.0	114B	92.7
88	26.0	115	88.9
90F	61.7	116	83.7
91	64.4	117	23.3
92	80.8	118	93.4
93	88.4	119	92.3
94	86.7	120	10.5
95	76.9	121C	13.2
96	29.3	122B	98.1
97	52.5	123D	70.8
98	35.6	124B	82.3
99	25.4	125B	95.1
100	77.2	126	91.4
101	72.6	127	79.9
102	74.5	128	96.0
103	70.0	129	37.9
104	86.1	130	16.7
105	81.6	131C	11.5
106	54.9	133B	85.8
107	68.8	134B	39.8
108	98.4		

As further demonstration of the efficacy of the described compounds as functional antagonists of endothelin, the ability of the described compounds to inhibit ET-1-induced phosphatidylinositol hydrolysis was measured.

Determination of Phosphatidylinositol (PI) Hydrolysis

MMQ cells (0.4 x 106 cells/mL) were labeled with 10 μCi/mL of [^{3}H]myo-inositol in RPMI for 16 hours. The cells were washed with PBS, then incubated with Buffer A containing protease inhibitors and 10 mM LiCl for 60 minutes. The cells were then incubated with test compounds for 5 minutes, and then challenged with 1 nM ET-1. ET-1 challenge was terminated by the addition of 1.5 mL of 1:2 (v/v) chloroform-methanol. Total inositol phosphates were extracted after adding chloroform and water to give final proportions of 1:1:0.9 (v/v/v) chloroform-methanol-water of as described by Berridge (Biochem. J. 206 587-595 (1982)). The upper aqueous phase (1 mL) was retained and a small portion (100 μL) was counted. The rest of the aqueous sample was analyzed by batch chromatography using anion-exchange resin AG1-X8 (Bio-Rad). The IC_{50} is the concentration of test compound required to inhibit the ET-induced increase in PI turnover by 50%. The data are shown in Table 2. The results of the above study clearly indicate that the compounds act as functional ET antagonists.

Table 2

Phosphatidylinositol Hydrolysis

Example	IC_{50} nM
27F	4.1
28	16
29	36
32	8.6
34	43
35	47
36	0.9
43B	1.3
44	4.6
93	4.9
94	4.2
109	3.6
110	2.6
111	0.9
114B	11
119	37
125B	53

As further demonstration of the efficacy of the described compounds as functional antagonists of endothelin, the ability of the described compounds to inhibit ET-1-induced constriction of vascular tissues was measured.

Functional Assay : ET-1 induced Vasoconstriction

Male New Zealand white rabbits (2.2-2.8 kg) were gassed with CO_2 until anesthetized and exsanguinated. The thoracic aorta or femoral artery was quickly removed and placed in a Krebs-Henseleit (KH) buffer gassed with 95/5 O_2/CO_2 to maintain pH at 7.4. The vessel was cleared of extraneous tissue, denuded of it's endothelium and

segmented into 4-5 mm wide rings which were suspended in 2 ml jacketed tissue baths maintained at 37 °C. Tissue baths had been siliconized to prevent adsorption of peptide to glass. Tissues were attached via gold chain to an isometric force transducer linked with a physiograph for monitoring tension changes. Baseline tension was set at 2.0 g (aorta) or 0.5 g (femoral artery) and the tissues allowed to equilibrate for 3 hrs. During this period, the tissues were washed every 15 minutes with fresh KH and the tension continually adjusted to baseline. Thirty minutes into the equilibration period, endothelial denudation of the vessels was confirmed by the lack of relaxation by acetylcholine (3 μM) of constriction by norepinephrine (1 μM).

Endothelin Dose-Response Curves (DRCs):

ET DRCs, 1E-12 to 1E-6 M, were performed establishing compound potency. Endothelin efficacy was measured against K^+ (55 mM) depolarization/constriction of the vessels at completion of the ET curves. Control ET-1 curves were performed along side ET-1 curves of tissues pretreated with ET antagonist. Vessel sets compared were from the same animal and thus, paired for analysis purposes.

Pretreatment Effects on Endothelin Responses: Pretreatment compounds (antagonists) were equilibrated 20 minutes prior to ET-1 DRCs.

Drug Potency Determination and Statistical Analysis: Data were compiled from individual experiments and means ± S.E. calculated. Control and antagonist treated curves were normalized and EC_{50}s for ET-1 contraction were calculated from logistically (non-linear regression) fitted curves generated by Allfit software. EC_{50} is the concentration of ET-1 necessary to cause 50% of the maximum constriction possible for the tissue rings.

The results from one compound are shown in Table 3.

Table 3

Example	Dose	EC_{50} nM
Control	No drug	3.1
1	10 μM	25.1

The data shows that in the presence of no drug, it takes 3 nM endothelin-1 to cause 50% of the maximum constriction of the tissue rings. In the presence of 10 μM of the product of Example 1, it takes a greater amount of endothelin-1 (the EC_{50} for endothelin-1 is shifted from 3.1 nM to 25.1 nM) to cause 50% maximal constriction, indicating that the product of Example 1 is an endothelin antagonist.

The ability of the compounds of the invention to lower blood pressure can be demonstrated according to the methods described in Matsumura, et al., Eur. J. Pharmacol. 185 103 (1990) and Takata, et al., Clin. Exp. Pharmacol. Physiol. 10 131 (1983).

The ability of the compounds of the invention to treat congestive heart failure can be demonstrated according to the method described in Margulies, et al., Circulation 82 2226 (1990).

The ability of the compounds of the invention to treat myocardial ischemia can be demonstrated according to the method described in Watanabe, et al., Circ. Res. 69 370 (1991).

The ability of the compounds of the invention to treat coronary angina can be demonstrated according to the method described in Heistad, et al., Circ. Res. 54 711 (1984).

The ability of the compounds of the invention to treat cerebral vasospasm can be demonstrated according to the methods described in Nakagomi, et al., J. Neurosurg. 66 915 (1987) or Matsumura, et al., Life Sci. 49 841-848 (1991).

The ability of the compounds of the invention to treat cerebral ischemia can be demonstrated according to the method described in Hara et al., Eur. J. Pharmacol. 197: 75-82, (1991).

The ability of the compounds of the invention to treat acute renal failure can be demonstrated according to the method described in Kon, et al., J. Clin. Invest. 83 1762 (1989).

The ability of the compounds of the invention to treat chronic renal failure can be demonstrated according to the method described in Benigni, et al., Kidney Int. 44 440-444 (1993).

The ability of the compounds of the invention to treat gastric ulceration can be demonstrated according to the method described in Wallace, et al., Am. J. Physiol. 256 G661 (1989).

The ability of the compounds of the invention to treat cyclosporin-induced nephrotoxicity can be demonstrated according to the method described in Kon, et al., Kidney Int. 37 1487 (1990).

The ability of the compounds of the invention to treat endotoxin-induced toxicity (shock) can be demonstrated according to the method described in Takahashi, et al., Clinical Sci. 79 619 (1990).

The ability of the compounds of the invention to treat asthma can be demonstrated according to the method described in Potvin and Varma, Can. J. Physiol. and Pharmacol. 67 1213 (1989).

The ability of the compounds of the invention to treat transplant-induced atherosclerosis can be demonstrated according to the method described in Foegh, et al., Atherosclerosis 78 229-236 (1989).

The ability of the compounds of the invention to treat atherosclerosis can be demonstrated according to the methods described in Bobik, et al., Am. J. Physiol. 258 C408 (1990) and/or Chobanian, et al., Hypertension 15 327 (1990).

The ability of the compounds of the invention to treat LPL-related lipoprotein disorders can be demonstrated according to the method described in Ishida, et al., Biochem. Pharmacol. 44 1431-1436 (1992).

The ability of the compounds of the invention to treat pulmonary hypertension can be demonstrated according to the methods described in Miyauchi, et al., Circ. Res. 73 887 (1993).

The ability of the compounds of the invention to treat cardiac hypertrophy can be demonstrated according to the methods described in Ito, et al., Circulation 89 2198 (1994).

The ability of the compounds of the invention to treat neointimal formation (restenosis) can be demonstrated according to the methods described in Douglas, et al., Circ. Res. 75 190 (1994).

The ability of the compounds of the invention to treat proliferative diseases can be demonstrated according to the methods described in Bunchman ET and CA Brookshire, Transplantation Proceed. 23 967-968 (1991); Yamagishi, et al., Biochem. Biophys. Res. Comm. 191 840-846 (1993); and/or Shichiri, et al., J. Clin. Invest. 87 1867-1871 (1991). Proliferative diseases include smooth muscle proliferation, systemic sclerosis, cirrhosis of the liver, adult respiratory distress syndrome, idiopathic cardiomyopathy, lupus erythematosus, diabetic retinopathy or other retinopathies, psoriasis, scleroderma or prostatic hyperplasia.

The compounds of the present invention can be used in the form of salts derived from inorganic or organic acids. These salts include but are not limited to the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, p-toluenesulfonate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as loweralkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides, and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and

phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid. Basic addition salts can be prepared *in situ* during the final isolation and purification of the compounds of formula (I), or separately by reacting the carboxylic acid function with a suitable base such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation or with ammonia, or an organic primary, secondary or tertiary amine. Pharmaceutically acceptable salts include, but are not limited to, cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, aluminum salts and the like, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. Other representative organic amines useful for the formation of base addition salts include diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like.

The compounds of the invention are useful for antagonizing endothelin in a human or other mammal. In addition, the compounds of the present invention are useful (in a human or other mammal) for the treatment of hypertension, pulmonary hypertension, Raynaud's disease, congestive heart failure, myocardial ischemia, reperfusion injury, coronary angina, cerebral ischemia, cerebral vasospasm, chronic or acute renal failure, pre-eclampsia (pregnancy-induced hypertension), non-steroidal antiinflammatory drug induced gastric ulceration, immunosuppressant (for example, cyclosporin or FK 506) induced nephrotoxicity, endotoxin-induced toxicity, asthma, fibrotic or proliferative diseases, including smooth muscle proliferation, systemic sclerosis, cirrhosis of the liver, adult respiratory distress syndrome,

idiopathic cardiomyopathy, lupus erythematosus, diabetic retinopathy or other retinopathies, psoriasis, scleroderma, prostatic hyperplasia, bladder dysfunction (for example, incontinence), cardiac hyperplasia, restenosis following arterial injury or other pathologic stenosis of blood vessels, LPL-related lipoprotein disorders, transplantation-induced atherosclerosis or atherosclerosis in general.

Total daily dose administered to a host in single or divided doses may be in amounts, for example, from 0.001 to 1000 mg/kg body weight daily and more usually 0.1 to 100 mg/kg for oral administration or 0.01 to 10 mg/kg for parenteral administration. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination, and the severity of the particular disease undergoing therapy.

The compounds of the present invention may be administered orally, parenterally, sublingually, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration may also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques.

Injectable preparations, for example, sterile injectable aqueous or oleagenous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or

solvent, for example, as a solution in 1,3-propanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols which are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

The compounds of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically aceptable and metabolizable lipid capabale of forming

liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and phosphatidyl cholines (lecithins), both natural and synthetic.

Methods to form liposomes are known in the art. See, for example, Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N.Y. (1976), p. 33 et seq.

While the compounds of the invention can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more cardiovascular agents independently selected from diuretics, adrenergic blocking agents, vasodilators, calcium channel blockers, renin inhibitors, angiotensin converting enzyme (ACE) inhibitors, angiotensin II antagonists, potassium channel activators and other cardiovascular agents.

Representative diuretics include hydrochlorothiazide, chlorothiazide, acetazolamide, amiloride, bumetanide, benzthiazide, ethacrynic acid, furosemide, indacrinone, metolazone, spironolactone, triamterene, chlorthalidone and the like or a pharmaceutically acceptable salt thereof.

Representative adrenergic blocking agents include phentolamine, phenoxybenzamine, prazosin, terazosin, tolazine, atenolol, metoprolol, nadolol, propranolol, timolol, carteolol and the like or a pharmaceutically acceptable salt thereof.

Representative vasodilators include hydralazine, minoxidil, diazoxide, nitroprusside and the like or a pharmaceutically acceptable salt thereof.

Representative calcium channel blockers include amrinone, bencyclane, diltiazem, fendiline, flunarizine, nicardipine, nimodipine, perhexilene, verapamil, gallopamil, nifedipine and the like or a pharmaceutically acceptable salt thereof.

Representative renin inhibitors include enalkiren, RO 42-5892, PD-134672 and the like or a pharmaceutically acceptable salt thereof.

Representative angiotensin II antagonists include DUP 753 and the like.

Representative ACE inhibitors include captopril, enalapril, lisinopril and the like or a pharmaceutically acceptable salt thereof.

Representative potassium channel activators include pinacidil and the like or a pharmaceutically acceptable salt thereof.

Other representative cardiovascular agents include sympatholytic agents such as methyldopa, clonidine, guanabenz, reserpine and the like or a pharmaceutically acceptable salt thereof.

The compounds of the invention and the antihypertensive agent can be administered at the recommended maximum clinical dosage or at lower doses. Dosage levels of the active compounds in the compositions of the invention may be varied so as to obtain a desired therapeutic response depending on the route of administration, severity of the disease and the response of the patient. The combination can be administered as separate compositions or as a single dosage form containing both agents.

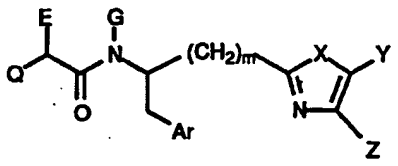
When administered as a combination, the therapeutic agents can be formulated as separate compositions which are given at the same time or different times, or the therapeutic agents can be given as a single composition.

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds, processes, compositions and methods. Variations and changes which are obvious to one skilled in the art are intended to be within the scope and nature of the invention which are defined in the appended claims.

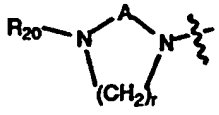
CLAIMS

What is claimed is:

1. A compound of the formula:



wherein m is 0, 1 or 2;
X is -N(R_2)-, -O- or -S-, wherein R_2 is hydrogen, loweralkyl, arylalkyl or (heterocyclic)alkyl;
Q is (1) R_1-A-N(B)- wherein
A is -C(O)- or -S(O)$_2$-;
R_1 is loweralkyl, cycloalkyl, cycloalkylalkyl, arylalkyl, aryl, alkoxy, arylalkoxy, cycloalkoxy, cycloalkylalkoxy, aryloxy, alkylamino, cycloalkylamino, arylamino, cycloalkylalkylamino, arylalkylamino, dialkylamino, diarylamino, (alkyl)cycloalkylamino, (alkyl)arylamino, (alkyl)cycloalkylalkylamino, (alkyl)arylalkylamino, heterocyclic, (heterocyclic)alkyl, (heterocyclic)amino, spirocarbocyclic or spiroheterocyclic; and
B is hydrogen or loweralkyl; or



(2) wherein A is as defined above and R_{20} is loweralkyl, cycloalkyl, cycloalkylalkyl, arylalkyl, aryl, heterocyclic, (heterocyclic)alkyl, spirocarbocyclic or spiroheterocyclic, and r is 2 to 4;

E is loweralkyl optionally substituted with one, two or three substituents independently selected from cyano, halo, hydroxy, alkoxy, amino, alkylamino, dialkylamino, thioalkoxy and azido;

G is hydrogen or loweralkyl;

E is loweralkyl optionally substituted with one, two or three substituents independently selected from cyano, halo, hydoxy, alkoxy, amino, alkylamino, dialkylamino, thioalkoxy and azido;

Ar is bicyclic aryl or bicyclic heteroaryl; and

Y and Z are independently selected from the group consisting of

(1) hydrogen;

(2) loweralkyl;

(3) loweralkyl substituted with one, two or three groups independently selected from cyano, hydroxy, alkoxy, amino, alkylamino, dialkylamino, azido, thioalkoxy, and halo;

(4) cycloalkyl;

(5) (cycloalkyl)alkyl;

(6) aryl;

(7) arylalkyl;

(8) a radical of the formula $-(CH_2)_n-C(O)-W$ wherein W is $-OR_{10}$, wherein R_{10} is hydrogen or a carboxy protecting group, amino, alkylamino, dialkylamino, hydroxyamino, N-hydroxyl-N-alkylamino or a naturally occurring α-amino acid wherein the amino acid is bonded through the α-amino group;

(9) a radical of the formula $-(CH_2)_n-V$ wherein V is

(a) $-S(O)_2NHC(O)R_{16}$ wherein R_{16} is loweralkyl, haloalkyl, or phenyl,

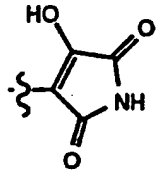
(b) $-PO_3H_2$,

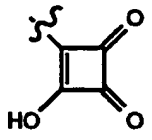
(c) -P(O)(OH)E wherein E is hydrogen, loweralkyl or arylalkyl,

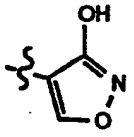
(d) -CN,

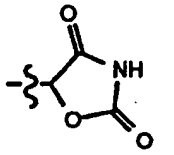
(e) $-C(O)NHR_{17}$ wherein R_{17} is loweralkyl,

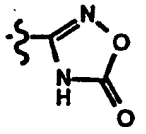
(f) alkylaminocarbonyl,
(g) dialkylaminocarbonyl,
(h) tetrazolyl,
(i) hydroxy,
(j) alkoxy,
(k) sulfonamido,
(l) $-C(O)NHS(O)_2R_{16}$ wherein R_{16} is defined as above,

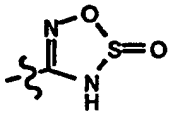
(m)  ,

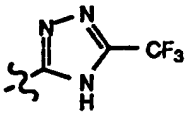
(n)  ,

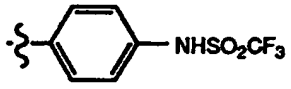
(o)  ,

(p)  ,

(q)  ,

(r)  ,

(s)  , or



(t) ; and

(10) $-(CH_2)_n-NHS(O)_2R_6$ wherein R_6 is loweralkyl or haloalkyl and wherein at each occurrence n as used above is independently selected from 0, 1 or 2;

with the proviso that at least one of Y and Z is a radical of the formula $-(CH_2)_n-C(O)-W$, $-(CH_2)_n-$(tetrazolyl) or $-(CH_2)_n-NHS(O)_2R_6$ wherein n, W and R_6 are defined as above;

or a pharmaceutically acceptable salt thereof.

2. A compound according to Claim 1 wherein

Q is $R_1-C(O)-N(B)-$;

Y is

(1) hydrogen;

(2) loweralkyl;

(3) loweralkyl substituted with one, two or three substituents independently selected from the group consisting of cyano, hydroxy, alkoxy, amino, alkylamino, dialkylamino, thioalkoxy, and halo;

(4) cycloalkyl;

(5) (cycloalkyl)alkyl;

(6) aryl;

(7) arylalkyl or

(8) a radical of the formula $-(CH_2)_n-C(O)-W$ wherein W is $-OR_{10}$ wherein R_{10} is hydrogen or a carboxy protecting group; and

Z is

(1) a radical of the formula $-(CH_2)_n-C(O)-W$ wherein W is $-OR_{10}$, wherein R_{10} is hydrogen or a carboxy protecting group, amino, alkylamino, dialkylamino, hydroxyamino, N-hydroxyl-N-alkylamino and a

naturally occurring α-amino acid wherein the amino acid is bonded through the α-amino group;

(2) $-(CH_2)_n$-(tetrazolyl) or

(3) $-(CH_2)_n-NHS(O)_2R_6$ wherein R_6 is loweralkyl or haloalkyl and at each occurrence n as used above is independently selected from 0, 1 or 2; or

Q is $R_1-C(O)-N(B)-$;

Y is

(1) a radical of the formula $-(CH_2)_n-C(O)-W$ wherein W is $-OR_{10}$, wherein R_{10} is hydrogen or a carboxy protecting group, amino, alkylamino, dialkylamino, hydroxyamino, N-hydroxyl-N-alkylamino or a naturally occurring α-amino acid wherein the amino acid is bonded through the α-amino group;

(2) $-(CH_2)_n$-(tetrazolyl) or

(3) $-(CH_2)_n-NHS(O)_2R_6$ wherein R_6 is loweralkyl or haloalkyl; and

Z is

(1) hydrogen;

(2) loweralkyl;

(3) loweralkyl substituted with one, two or three substituents independently selected from the group consisting of cyano, hydroxy, alkoxy, amino, alkylamino, dialkylamino, thioalkoxy, and halo;

(4) cycloalkyl;

(5) (cycloalkyl)alkyl;

(6) aryl;

(7) arylalkyl or

(8) a radical of the formula $-(CH_2)_n-C(O)-W$ wherein W is $-OR_{10}$ wherein R_{10} is hydrogen or a carboxy protecting group and at each occurrence n as used above is independently selected from 0, 1 or 2;

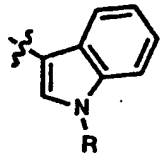
or a pharmaceutically acceptable salt thereof.

3. A compound according to Claim 1 wherein

Q is R_1-C(O)-N(B)- wherein R_1 is loweralkyl, (alkyl)cycloalkylamino, cycloalkoxy, arylamino, (alkyl)arylamino, diarylamino, cycloalkyl, cycloalkylalkyl, arylalkyl, arylalkoxy, cycloalkylalkylamino, cycloalkylamino, alkoxy, arylalkylamino, dialkylamino, spiroheterocyclic or heterocyclic, and B is hydrogen or methyl;

E is isobutyl;

G is hydrogen;

Ar is  wherein R is hydrogen or methyl;

Y is hydrogen, arylalkyl, haloalkyl, loweralkyl, aryl or cycloalkyl;

Z is a radical of the formula $-(CH_2)_n$-CO-W, wherein W is $-OR_{10}$, wherein R_{10} is hydrogen or a carboxy protecting group, alkylamino, hydroxyamino or a naturally occurring α-amino acid wherein the amino acid is bonded through the α-amino group or $-(CH_2)_n$-(tetrazolyl) wherein n as used above is 0 or 1;

m is 0 or 1; and

X is $-N(R_2)-$, -O- or -S- wherein R_2 is hydrogen or loweralkyl;

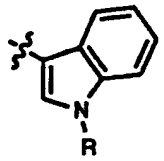
or a pharmaceutically acceptable salt thereof.

4. A compound according to Claim 1 wherein

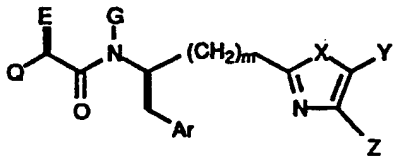
Q is R_1-C(O)-N(B)- wherein R_1 is cycloalkylamino, arylamino, arylalkyl, spiroheterocyclic, heterocyclic, (alkyl)arylamino, cycloalkoxy, or (alkyl)cycloalkylamino and B is hydrogen or methyl;

E is isobutyl;

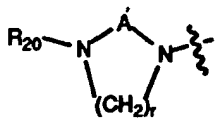
G is hydrogen;

Ar is  wherein R is hydrogen or methyl;
m is 0;
X is -NH- or -O- ;
Y is loweralkyl; and
Z is $-CO_2H$;
or a pharmaceutically acceptable salt thereof.

5. A compound of the formula:



wherein m is 0, 1 or 2;
X is $-N(R_2)-$, -O- or -S-, wherein R_2 is hydrogen, loweralkyl, arylalkyl or (heterocyclic)alkyl;
Q is (1) R_1-A-N(B)- wherein
A is $-C(O)-$ or $-S(O)_2-$;
R_1 is loweralkyl, cycloalkyl, cycloalkylalkyl, arylalkyl, aryl, alkoxy, arylalkoxy, cycloalkoxy, cycloalkylalkoxy, aryloxy, alkylamino, cycloalkylamino, arylamino, cycloalkylalkylamino, arylalkylamino, dialkylamino, diarylamino, (alkyl)cycloalkylamino, (alkyl)arylamino, (alkyl)cycloalkylalkylamino, (alkyl)arylalkylamino, heterocyclic, (heterocyclic)alkyl, (heterocyclic)amino, spirocarbocyclic or spiroheterocyclic; and
B is hydrogen or loweralkyl; or

(2)  wherein A is as defined above and R_{20} is loweralkyl, cycloalkyl, cycloalkylalkyl, arylalkyl, aryl, heterocyclic, (heterocyclic)alkyl, spirocarbocyclic or spiroheterocyclic, and r is 2 to 4;

G is hydrogen or loweralkyl;

E is loweralkyl optionally substituted with one, two or three substituents independently selected from the group consisting of cyano, halo, hydoxy, alkoxy, amino, alkylamino, dialkylamino, thioalkoxy and azido;

Ar is bicyclic aryl or bicyclic heteroaryl;

Y and Z are independently selected from the group consisting of

(1) hydrogen;

(2) loweralkyl;

(3) loweralkyl substituted with one, two or three groups independently selected from the group consisting of cyano, hydroxy, alkoxy, amino, alkylamino, dialkylamino, azido, thioalkoxy, and halo;

(4) cycloalkyl;

(5) (cycloalkyl)alkyl;

(6) aryl;

(7) arylalkyl;

(8) a radical of the formula $-(CH_2)_n-C(O)-W$ wherein W is $-OR_{10}$, wherein R_{10} is hydrogen or a carboxy protecting group, amino, alkylamino, dialkylamino, hydroxyamino, N-hydroxyl-N-alkylamino or a naturally occurring α-amino acid wherein the amino acid is bonded through the α-amino group;

(9) a radical of the formula $-(CH_2)_n-V$ wherein V is

(a) $-S(O)_2NHC(O)R_{16}$ wherein R_{16} is loweralkyl, haloalkyl, or phenyl,

(b) $-PO_3H_2$,

(c) -P(O)(OH)E wherein E is hydrogen, loweralkyl or arylalkyl,

(d) -CN,

(e) -C(O)NHR$_{17}$ wherein R$_{17}$ is loweralkyl,

(f) alkylaminocarbonyl,

(g) dialkylaminocarbonyl,

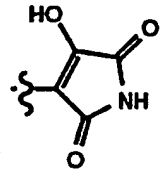
(h) tetrazolyl,

(i) hydroxy,

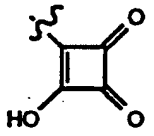
(j) alkoxy,

(k) sulfonamido,

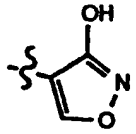
(l) -C(O)NHS(O)$_2$R$_{16}$ wherein R$_{16}$ is defined as above,

(m) 

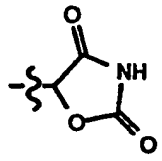
,

(n) 

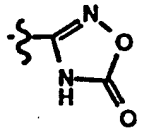
,

(o) 

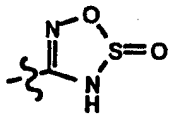
,

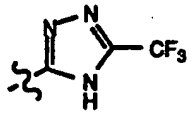
(p) 

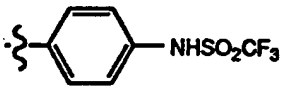
,

(q) 

,

(r)  ,

(s)  , or

(t)  ; and

(10) $-(CH_2)_n-NHS(O)_2R_6$ wherein R_6 is loweralkyl or haloalkyl and wherein at each occurrence n as used above is independently selected from 0, 1 or 2;

with the proviso that one of Y and Z is a radical of the formula $-(CH_2)_n-C(O)-W$, $-(CH_2)_n-$(tetrazolyl) or $-(CH_2)_n-NHS(O)_2R_6$ wherein n, W and R_6 are defined as above;

or a pharmaceutically acceptable salt thereof.

6. A compound according to Claim 5 wherein

Q is $R_1-C(O)-N(B)-$;

Y is

(1) hydrogen;

(2) loweralkyl;

(3) loweralkyl substituted with one, two or three substituents independently selected from the group consisting of cyano, hydroxy, alkoxy, amino, alkylamino, dialkylamino, thioalkoxy, and halo;

(4) cycloalkyl;

(5) (cycloalkyl)alkyl;

(6) aryl;

(7) arylalkyl or

(8) a radical of the formula $-(CH_2)_n-C(O)-W$ wherein W is $-OR_{10}$ wherein R_{10} is hydrogen or a carboxy protecting group; and

Z is

(1) a radical of the formula $-(CH_2)_n-C(O)-W$ wherein W is $-OR_{10}$, wherein R_{10} is hydrogen or a carboxy protecting group, amino, alkylamino, dialkylamino, hydroxyamino, N-hydroxyl-N-alkylamino and a naturally occurring α-amino acid wherein the amino acid is bonded through the α-amino group;

(2) $-(CH_2)_n$-(tetrazolyl) or

(3) $-(CH_2)_n-NHS(O)_2R_6$ wherein R_6 is loweralkyl or haloalkyl and n as used above is 0, 1 or 2; or

Q is $R_1-C(O)-N(B)-$;

Y is

(1) a radical of the formula $-(CH_2)_n-C(O)-W$ wherein W is $-OR_{10}$, wherein R_{10} is hydrogen or a carboxy protecting group, amino, alkylamino, dialkylamino, hydroxyamino, N-hydroxyl-N-alkylamino or a naturally occurring α-amino acid wherein the amino acid is bonded through the α-amino group;

(2) $-(CH_2)_n$-(tetrazolyl) or

(3) $-(CH_2)_n-NHS(O)_2R_6$ wherein R_6 is loweralkyl or haloalkyl and n as used above is 0, 1 or 2; and

Z is

(1) hydrogen;

(2) loweralkyl;

(3) loweralkyl substituted with one, two or three substituents independently selected from the group consisting of cyano, hydroxy, alkoxy, amino, alkylamino, dialkylamino, thioalkoxy, and halo;

(4) cycloalkyl;

(5) (cycloalkyl)alkyl;

(6) aryl;

(7) arylalkyl or

(8) a radical of the formula $-(CH_2)_n-C(O)-W$ wherein W is $-OR_{10}$ wherein R_{10} is hydrogen or a carboxy protecting group;

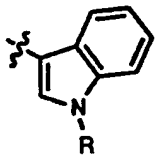
or a pharmaceutically acceptable salt thereof.

7. A compound according to Claim 5 wherein

Q is $R_1-C(O)-N(B)-$ wherein R_1 is loweralkyl, (alkyl)cycloalkylamino, cycloalkoxy, arylamino, (alkyl)arylamino, diarylamino, cycloalkyl, cycloalkylalkyl, arylalkyl, arylalkoxy, cycloalkylalkylamino, cycloalkylamino, alkoxy, arylalkylamino, dialkylamino, spiroheterocyclic or heterocyclic, and B is hydrogen or methyl;

E is isobutyl;

G is hydrogen;

Ar is  wherein R is hydrogen or methyl;

Y is hydrogen, arylalkyl, haloalkyl, loweralkyl, aryl or cycloalkyl;

Z is a radical of the formula $-(CH_2)_n-CO-W$, wherein W is $-OR_{10}$, wherein R_{10} is hydrogen or a carboxy protecting group, alkylamino, hydroxyamino or a naturally occurring α-amino acid wherein the amino acid is bonded through the α-amino group or $-(CH_2)_n-$(tetrazolyl) wherein n as used above is 0 or 1;

m is 0 or 1; and

X is $-N(R_2)-$, $-O-$ or $-S-$ wherein R_2 is hydrogen or loweralkyl;

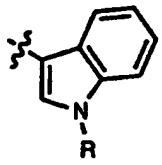
or a pharmaceutically acceptable salt thereof.

8. A compound according to Claim 5 wherein

Q is $R_1-C(O)-N(B)-$ wherein R_1 is cycloalkylamino, arylamino, arylalkyl, spiroheterocyclic, heterocyclic, (alkyl)arylamino, cycloalkoxy, or (alkyl)cycloalkylamino and B is hydrogen or methyl;

E is isobutyl;

G is hydrogen;

Ar is  wherein R is hydrogen or methyl;
m is 0;
X is -NH- or -O- ;
Y is loweralkyl; and
Z is $-CO_2H$;
or a pharmaceutically acceptable salt thereof.

9. A compound selected from the group consisting of:

2-{(1R)-1-(N-(Cyclohexylaminocarbonyl)-Leucyl-amino)-2-(indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid;
2-{(1R)-1-(N-(Cyclohexylaminocarbonyl)-Leucyl-amino)-2-(1-methyl-indol-3-yl)ethyl)-5-methyl-imidazole-4-carboxylic acid;
2-{(1R)-1-(N-(*endo*-2-Norbornylaminocarbonyl)-Leucyl-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid;
2-{(1R)-1-(N-(*exo*-2-Norbornylaminocarbonyl)-Leucyl-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid;
2-{(1R)-1-((N-Cyclopentylaminocarbonyl)-Leucyl-amino)-2-(1-methyl-indol-3-yl)ethyl)-5-methyl-imidazole-4-carboxylic acid;
2-{(1R)-1-(N-(Phenylaminocarbonyl)-Leucyl-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-imidazole-4-carboxylic acid;
2-{(1R)-1-(N-(N-Cyclohexylaminocarbonyl-N-methyl-Leucyl)-amino)-2-(1-methyl-indol-3-yl)ethyl]-5-methyl-imidazole-4-carboxylic acid;
2-{(1R)-1-(N-(4-Methoxyphenylacetyl)-Leucyl-amino)-2-(indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-(N-(1-oxa-4-azaspiro(5.4)decane-4-carbonyl)-Leucyl-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;
2-{(1R)-1-(N-(1-Indolinylcarbonyl)-Leucyl-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(Decahydroquinolin-1-ylcarbonyl)-Leucyl-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(1,2,3,4-Tetrahydroquinolin-1-ylcarbonyl)-Leucyl-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(N-Methyl-N-phenylaminocarbonyl)-Leucyl-amino)-2-(1-methyl-indol-3-yl)ethyl)-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(2-Hydroxyphenylaminocarbonyl)-Leucyl-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(Cyclohexyloxycarbonyl)-Leucyl-amino)-2-(1-methyl-indol-3-yl)ethyl}-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(N-Cyclohexylaminocarbonyl-N-methyl-Leucyl)-amino)-2-(1-methyl-indol-3-yl)ethyl)-5-methyl-oxazole-4-carboxylic acid;

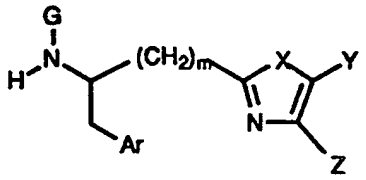
2-{(1R)-1-(N-(Phenylaminocarbonyl)-Leucyl-amino)-2-(1-methyl-indol-3-yl)ethyl)-5-methyl-oxazole-4-carboxylic acid;

2-{(1R)-1-(N-(3-Fluorophenylaminocarbonyl)-Leucyl-amino)-2-(1-methyl-indol-3-yl)ethyl)-5-methyl-oxazole-4-carboxylic acid; and

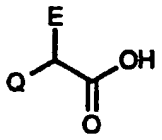
2-{(1R)-1-(N-(2-Fluorophenylaminocarbonyl)-Leucyl-amino)-2-(1-methyl-indol-3-yl)ethyl)-5-methyl-oxazole-4-carboxylic acid;

or a pharmaceutically acceptable salt thereof.

10. A process for preparing the compound of Claim 1 comprising reacting a compound of the formula:



wherein Ar, G, X, Y, Z and m are as defined therein with a compound of the formula:



or an activated derivative thereof
wherein Q and E are as defined in Claim 1.

11. A pharmaceutical composition for antagonizing endothelin comprising a therapeutically effective amount of the compound of Claim 1 or 5 and a pharmaceutically acceptable carrier.

12. A method for antagonizing endothelin comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1 or 5.

13. A method for treating treating hypertension, pulmonary hypertension, congestive heart failure, restenosis following arterial injury, fibrotic diseases, cerebral vasospasm, cardiac hypertrophy, cerebral or myocardial ischemia or atherosclerosis comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1 or 5.

14. A method for treating treating hypertension, pulmonary hypertension, congestive heart failure, restenosis following arterial injury, fibrotic diseases, cerebral vasospasm, cardiac hypertrophy, cerebral or myocardial ischemia or atherosclerosis comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1 or 5 in combination with one or more cardiovascular agents.

INTERNATIONAL SEARCH REPORT

Inter. nal Application No
PCT/US 94/10049

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D403/14 A61K31/41 C07D417/14 C07D413/14 C07D403/06
C07D417/06 C07D413/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 460 679 (BANYU PHARMACEUTICAL CO.) 11 December 1991	

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 December 1994	13.01.95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	De Jong, B

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte .onal Application No
PCT/US 94/10049

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0460679	11-12-91	AU-B-	632695	07-01-93
		AU-A-	7818291	12-12-91
		JP-A-	5178891	20-07-93